OSTEOPOROSIS

Constituents of bone

- Inorganic-65%
  - Hydroxyapatite
  - CaPo4
  - Ca citrate
  - Fluoride, Na,Mg,K
- Organic-25%
- Water -10%
  - Cells -4%
  - Matrix-21%

Osteoblast

- From marrow cells of stroma
- Contains ALP
- VIT D3 & PTH receptors
- Role in mineralisation
- Regulate osteoclast

Osteoclast

- Source- Monocytes
- Function- resorption of living bone
- Contains- Tartrate resistant acid phosphatase & Carbonic anhydrase

Remodeling

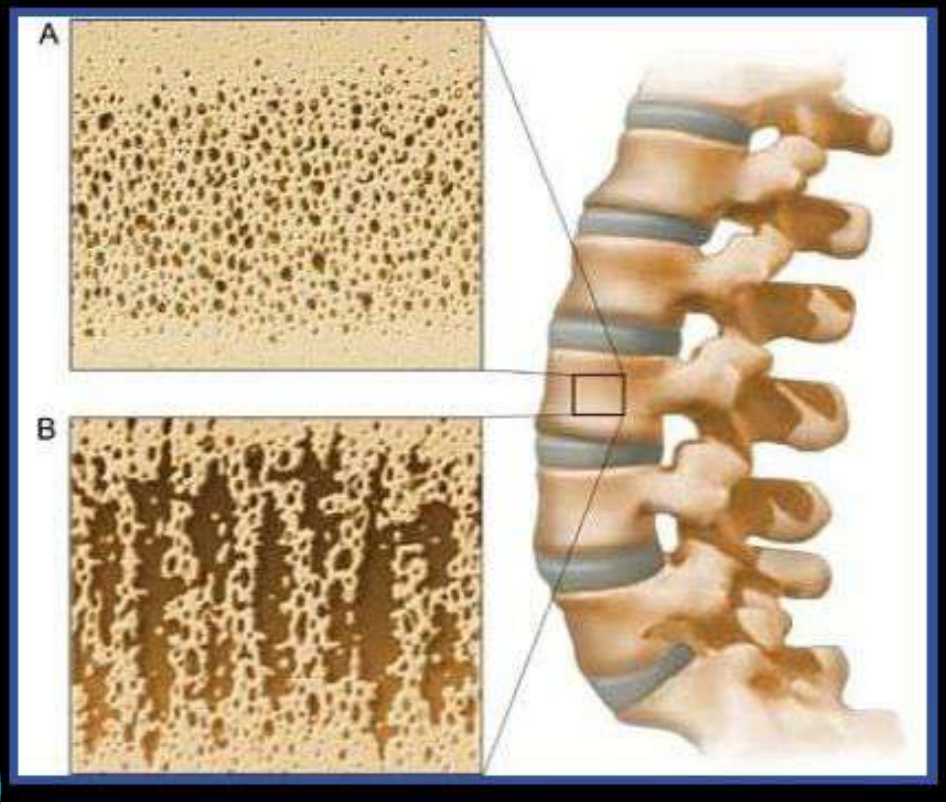
- Includes bone formation & resorbtion
- Initiated by osteoclast
- Followed by osteoblast
- Occur at same anatomical localisation
- Increases strength of bone
- Repair microdamage

Definition

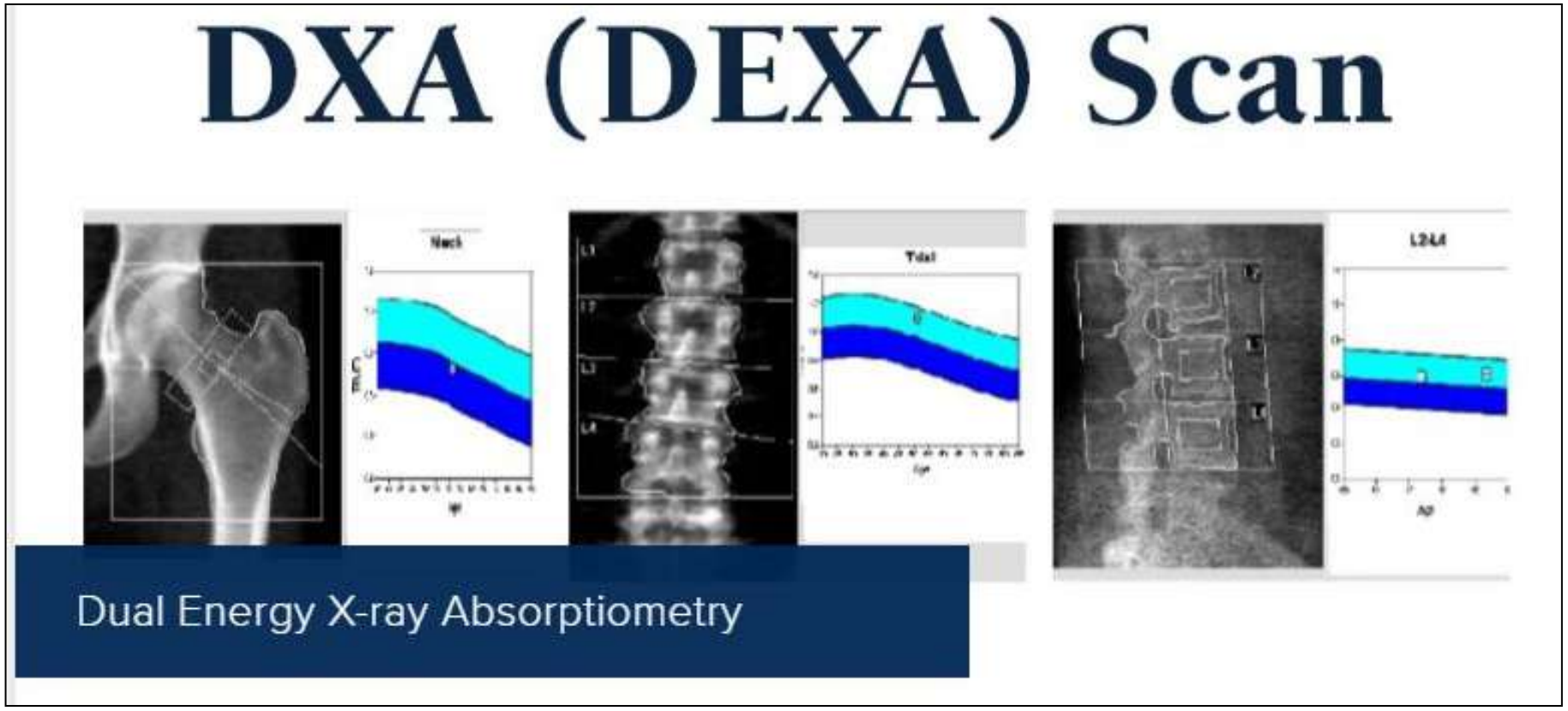
- Bone disease in which **bone tissue is normally mineralised** but the **amount of bone is decreased** & the structural integrity of trabecular bone is impaired & cortical bone becomes more porous and thinner.

Bone Mineral Density

- Defined as the amount of mineral matter (calcium) present per square centimetre of bone



How to measure your -Bone Mineral Density?



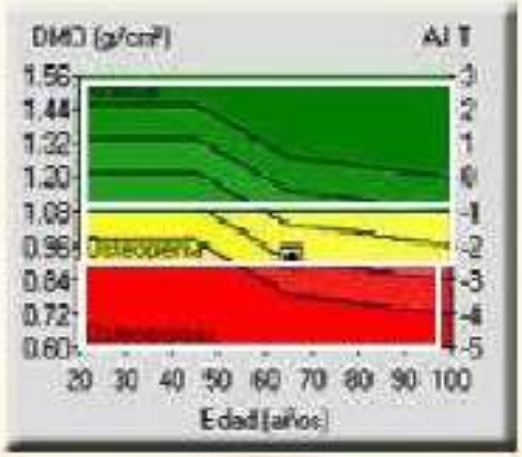
- Measures the amount of X-rays that have passed through your body.

- **Compares your bone density** with the bone density

- The difference between your measurement and that of a young healthy adult - **T score**.

- The difference between your measurement and that of someone of the same age **- Z score**.

WHO Classification of BMD using (DEXA) scan



Normal

- T score ≥ -1

Osteopenia

- T score -1 to -2.5

Osteoporosis

- T score < -2.5

Severe Osteoporosis

- T score < -2.5
- \+ H. of fracture

T score represents the number of SD a patient is above or below the mean BMD of a young adult.

Osteoporosis

- T score < -2.5
- Z score is below -2

Risk factors

Non modifiable

- Female sex
- Advanced age

Modifiable

- Smoking
- Alcholism
- Low body wt.
- Low Ca diet
- Estrogen defeciency
- Lack of physical activity

Classification-Nordin(1964)

Generalized

- Primary
- Secondary

Localized

- **Primary**(Riggs & Melton(1988))
- Type 1
- Type2

Type1
(Post menopausal)

- 51-70 yrs
- Sex ratio **F:M- 5:2**
- Mainly **trabecular bone**
- **Vertebral # more common**
- PTH decreased
- Ca absorption decreased
- Cause – related to menopause

Type 2
(Senile)

- **> 70 yrs**
- Sex ratio **2:1**
- Both **cortical & trabecular bone**
- Mainly **# NOF & inter trochantric #**
- PTH increased
- Ca absorbtion dec.
- Cause related to aging

Secondary osteoporosis

- **Hormonal**
- Hypo gonadism
- Hyper adrenocortical conditions
- Thyrotoxicosis
- Hyper prolactinimia
- DM

Nutritional

- Ca deficiency
- Malabsorbtion
- Malnutrition
- Alcoholism
- Scurvy
- Liver disease
- Vit D defeciency

Drugs

- Glucocorticoids
- Thyroxine excess
- Anticonvulsants
- Heparin
- Cytotoxic drugs
- Alcohol
- Lithium

Other causes

- Multiple myeloma
- Rhuematoid arthritis
- Mastocytosis
- Thalassemia
- pregnancy

Localised osteoporosis

a) Disuse osteoporosis
b) Sudecks osteodystrophy
c) Transient osteoporosis
d) Regional migratory osteoporosis
e) Idiopathic chondrolysis of hip

Diagnosis of osteoporosis

- **C/F**
- Low back ache-usually mild
- Loss of height
- Thoracic kyphosis
- # ‘s

Fractures

- Vertebral # ‘s
- Minimal symptoms
- Severe pain-r/o myeloma & other pathologies
- MC – lower thoracic ,upper lumbar(T/L jn)
- Usually T12 compression #
- Leads to thoracic kyhosis

Hip

- 50% intertrochantric
- Trochantric # more related to BMD
- NOF more related to mechanical factors

Physical examination

- Careful measurement of ht.
- Detection of kyphosis(rounded kyphosis)
- Blue sclera ,thin skin (O I)
- Hepatosplenomegaly (systemic disease)
- Skin pigmentation (cushings synd.)

Lab evaluations

- All routine investigations

- CBC,ESR
- Serum **Ca** & **P.**,**Alk phosphatase**
- LFT,RFT
- Blood sugar
- **S.PTH**
- **S.25-OH vitamin D**

- **For secondary causes :**
- TFT
- Serum testosterone/gonadotropin/prolactin

Radiological

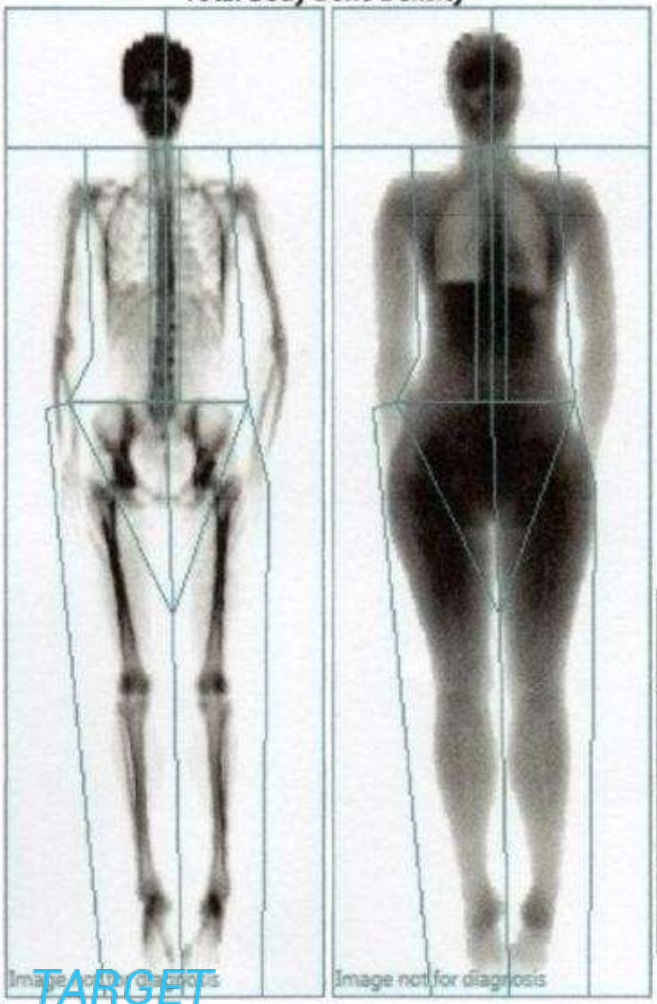
- DXA & DXA assisted techniques
- DXA – most common for determining bone mineral mass in unit CSA of bone
- 2 X-ray beams with different energy levels
- Targeted at specific region in skeleton
- Image determined after subtracting the soft tissue
- Then converts calculated density in gm/cm2 to T score in terms of SDs.

- T score is site, gender & technique dependent
- Z score is age & gender matched bone density reference value
- Quick & non invasive
- Low radiation dose
- Precision error : 1 to 2.5%
- Inexpensive ,harmless

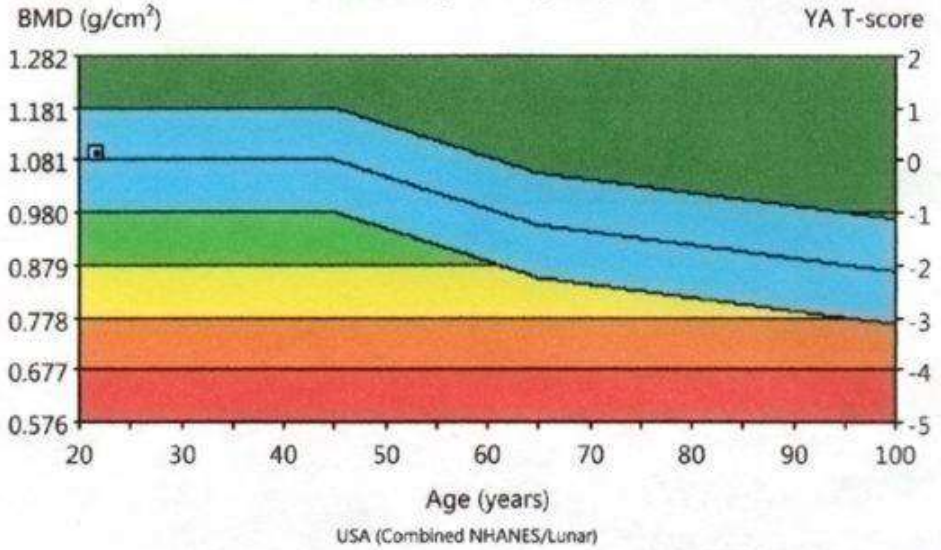
Who needs?

- Women > 65years
- Women <65 & risk factors for fragile fractures
- Premenopausal women with clinical signs of hypoestrogenemia
- Men >70
- Men < 70 + risk factors for fragile fractures
- Unexplained fragile fractures
- On chronic steroid therapy

Total Body Bone Density



Total Body: Total (BMD)



Densitometry: USA (Combined NHANES/Lunar) (Enhanced Analysis)

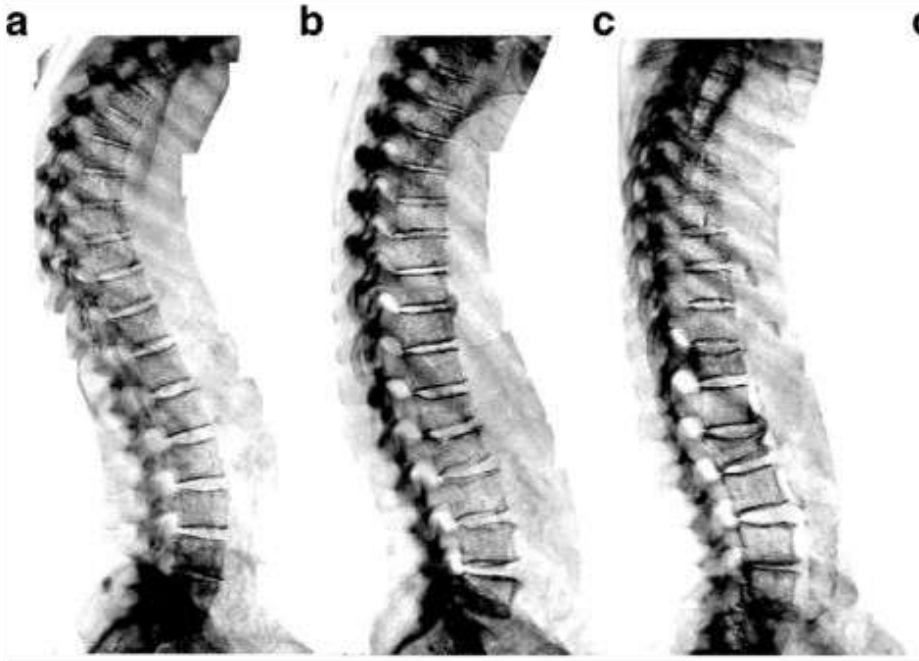
Region	BMD (g/cm²)	YA T-score	AM Z-score
Head	2.223	-	-
Arms	0.830	-	-
Legs	1.057	-	-
Trunk	0.880	-	-
Ribs	0.708	-	-
Spine	0.971	-	-
Pelvis	0.970	-	-
Total	1.096	0.2	0.2

VFA

- Vertebral fracture assessment
- Scan entire DL spine for assessing vertebral heights
- Densitometric **lateral imaging of spine**
- Permits evaluation of spine fractures without a lateral x ray

VFA

- Anterior, middle & posterior vertebral body dimensions of D4 to L4
- Diagnose pattern of vertebral fractures
- Pts who were classified as osteopenic / Normal based on T score > -2.5 were diagnosed as osteoporotic because of fractures.



d

HR-pQCT	Radius	Tibia
	% (normalized to age- and sex-specific reference values)	
Tt.BMD	60.70	95.97
Tb.N	73.55	86.41
Tb.Sp	144.49	120.88
Tb.Th	82.94	86.37

Advantage

- Very low radiation dose
- 2-50 Vs 600 micro SV in conventional x ray

Disadvantage

- Low resolution
- Less reliable to diagnose mild vertebral fractures
- Cant replace conventional lateral x rays which detects other pathologies also

TABLE 1. Imaging of spine for detection of VFs

Imaging method	Resolution	Radiation	Availability	Convenience	Cost
X-ray	+++	++	++	++	++
CT	+++	+++	+	+	+++
MRI	+++	0	+	+	+++
Nuclear scan	+	++	+	+	+++
VFA	++	+	+++	+++	+

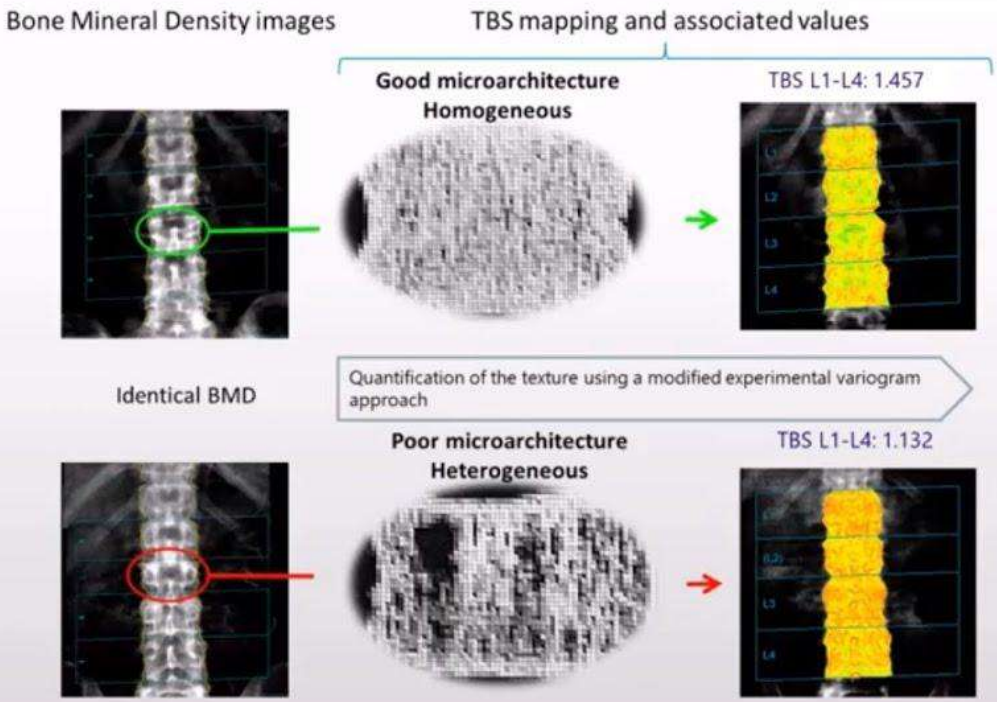
+++, High; ++, medium; +, low; 0, none.

Trabecular bone score

- Gray level textural index
- Obtained from L spine DXA images
- Using a dedicated software
- To assess vertebral trabecular microstructure
- TBS has no unit

TBS : Trabecular Bone Score

Texture parameter that is correlated to bone microarchitecture



- High TBS – normal bone
- Low – osteoporotic
- reported for each vertebra as well as for total spine
- Fractured or abnormal vertebrae are excluded
- Both prevalent and incident fragility fractures in postmenopausal women- low TBS

Use of DXA in monitoring treatment

- Correlation b/w change in BMD with therapy & reduction of fracture risk
- **Drugs □ reduce fracture risk, but not increase the bone density**
- Women >65 would continue to loose bone if untreated
- **A stable BMD on treatment= successful treatment**

X-RAY evaluation

- In diagnosis of OP fractures
- Loss of height of vertebrae
- **Rarefactions and loss of trabeculae** in hip and spine
- **Biconvex shape of vertebra** end plates
- **Pencil thinning of cortices of long bones**
- Vaccum phenomenon

- Exposure – 600microSv
- Lack sensitivity to detect early changes
- Reveals bone loss only after 25-30% bone density is lost
- **Digital x rays may b difficult to diagnose**

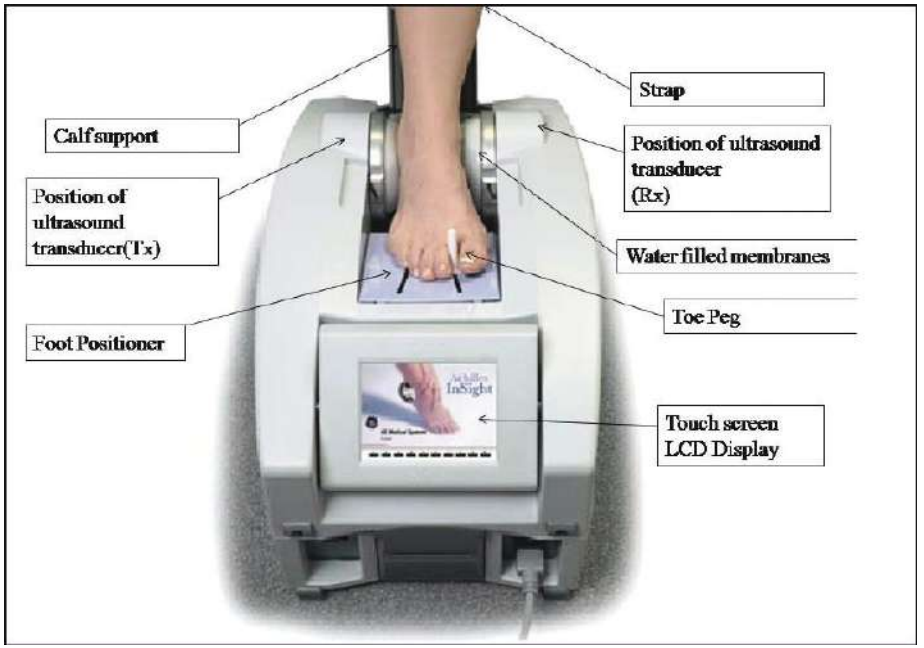
Quantitative CT

- Density measured in HU is converted into BMD
- Measured in volume (in hydroxyapetite/cm2)
- Performed on L1,L2,L3 & proximal femur
- Advantage : measure volumetrically
- **Independent of body size**

Quantitative ultra sound

- Broadband US attenuation
- Measure the calcaneum as it is a site with high metabolic turnover
- Low cost
- In children with risk of osteoporosis

Quantitative Ultrasound (QUS)



EOS

- Biplane X ray imaging system
- Predicts bone strength
- Assess 3D geometry & BMD with a single low dose X ray device

Bone mineral density assessment using the EOS® low-dose X-ray device: a feasibility study

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Abstract: To predict bone strength in the case of osteoporosis, it could be a real benefit to assess the three-dimensional (3D) geometry and the bone mineral density (BMD) with a single low-dose X-ray device, such as the EOS system (Biospace Med, Paris, France). EOS 3D reconstructions of the spine have already been validated. Thus, this study aims at evaluating the accuracy of this low-dose system as a densitometer first *ex vivo*.

The European Spine Phantom (ESP) (number 129) was scanned ten times using both the EOS and a Hologic device (Hologic, Inc., Massachusetts, USA). Accuracy was given by the sum of the systematic error (difference between BMDs assessed and true values given by the phantom manufacturer) and the random error (coefficient of variation). EOS BMDs and Hologic BMDs of 41 *ex-vivo* vertebrae were calculated and compared. The reproducibility of the method evaluating the EOS BMD was assessed giving the coefficient of variation of three measurements of the 41 vertebrae.

The accuracy of the EOS system is below 5.2 per cent, versus 7.2 per cent for the Hologic system in the same conditions. EOS BMDs are significantly higher than Hologic BMDs, but they are strongly correlated. The reproducibility of the method of assessment is equal to 0.95 per cent.

The EOS system is accurate for *ex-vivo* BMD assessments, which is promising regarding the use of this new system to predict vertebral strength.

Keywords: biomechanics, vertebra, osteoporosis, bone mineral density, bone strength prediction

1 INTRODUCTION

Osteoporosis was defined in the past by low bone mass and micro-architectural deterioration of bone tissue, resulting in an increase in skeletal fragility and fracture susceptibility [1]. A low bone mineral density (BMD) does not always explain prevalent vertebral fracture, suggesting that other parameters have to be taken into account. Thus, a new definition of osteoporosis was proposed recently, on the basis of the global notion of 'bone strength' [2]. Mathematical models combining three-demensional (3D) geometrical parameters with BMD have been used in the past to predict the bone strength with a limited efficiency [3–6]. Recently, mechanical approaches based on finite element (FE) models have been proposed to predict strength of osteoporotic vertebrae or effects of vertebral tumours [7–12]. To be accurate, the FE models should integrate the real 3D geometry of the vertebra and subject-specific mechanical properties such as Young's modulus. The mechanical properties are assessed as a result of relationships with BMD. Voxel-based FE models well predict vertebral strength *ex vivo* (r^2 between 0.79 and 0.94) [7–9, 11]. Unfortunately, they are based on quantitative computed tomography (QCT) acquisitions and cannot be used to analyse the whole spine *in vivo* for patients' follow-up because of the high radiation dose. Thus, special attention should be paid to low-dose X-ray devices, such as the EOS® imaging device (Biospace Med, Paris, France). This system takes simultaneously two perpendicular

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Bone turnover markers

- **Analyze the collagen degradation products**
- Reflecting the **osteoclastic activity**
- **Collagen or non collagenous proteins**
- Bone specific ALP (TAP & BAP)
- Osteocalcin
- PINP/PICP
- **Elevated – predicts accelerated bone loss**

Newer biomarkers

- Studies on mi RNA
- Small noncoding circulating RNA s

Goals of treatment

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

NON-pharmacological measures

- Maintain adequate **protein intake**
- Use proper body mechanics
- **Exercise & sun light exposure**
- Consider use of hip protectors in individuals with high fall risk
- Protective pads worn around the outer thigh
- **Take measures to reduce fall risk**

Nutritional Recommendations

TABLE 3: Recommended dietary allowance (RDA) of calcium for Indians[27,30]

Group	Calcium (mg/day)
Adult women	600
Pregnant women	1,200
Lactating women	1,200
Postmenopausal women	800
Men	600

Optimal calcium intake reduces bone loss and suppresses bone turnover.

TABLE 4: Recommended dietary allowance (RDA) of vitamin D[31]

Group	RDA (IU)	Upper limit
Adults (18 years and above)	1,500–2,000	10,000
Pregnant and lactating women	1,500–2,000	10,000
Children and adults at risk*	2–3 times the normal requirement for their age	

*At risk = Obesity, HIV, on glucocorticoid, anticonvulsant, antifungal and antiviral therapy

Pharmacologic treatment of osteoporosis indications

- **Presenting with typical osteoporosis related fractures** (certainly hip and spine), in the setting of a BMD in the low bone mass or osteoporosis range
- **BMD T-Score is ≤–2.5,**
- In **postmenopausal women with fracture** or multiple risk factors **even if BMD is not in the osteoporosis range**

Pharmacologic Treatment Of Osteoporosis

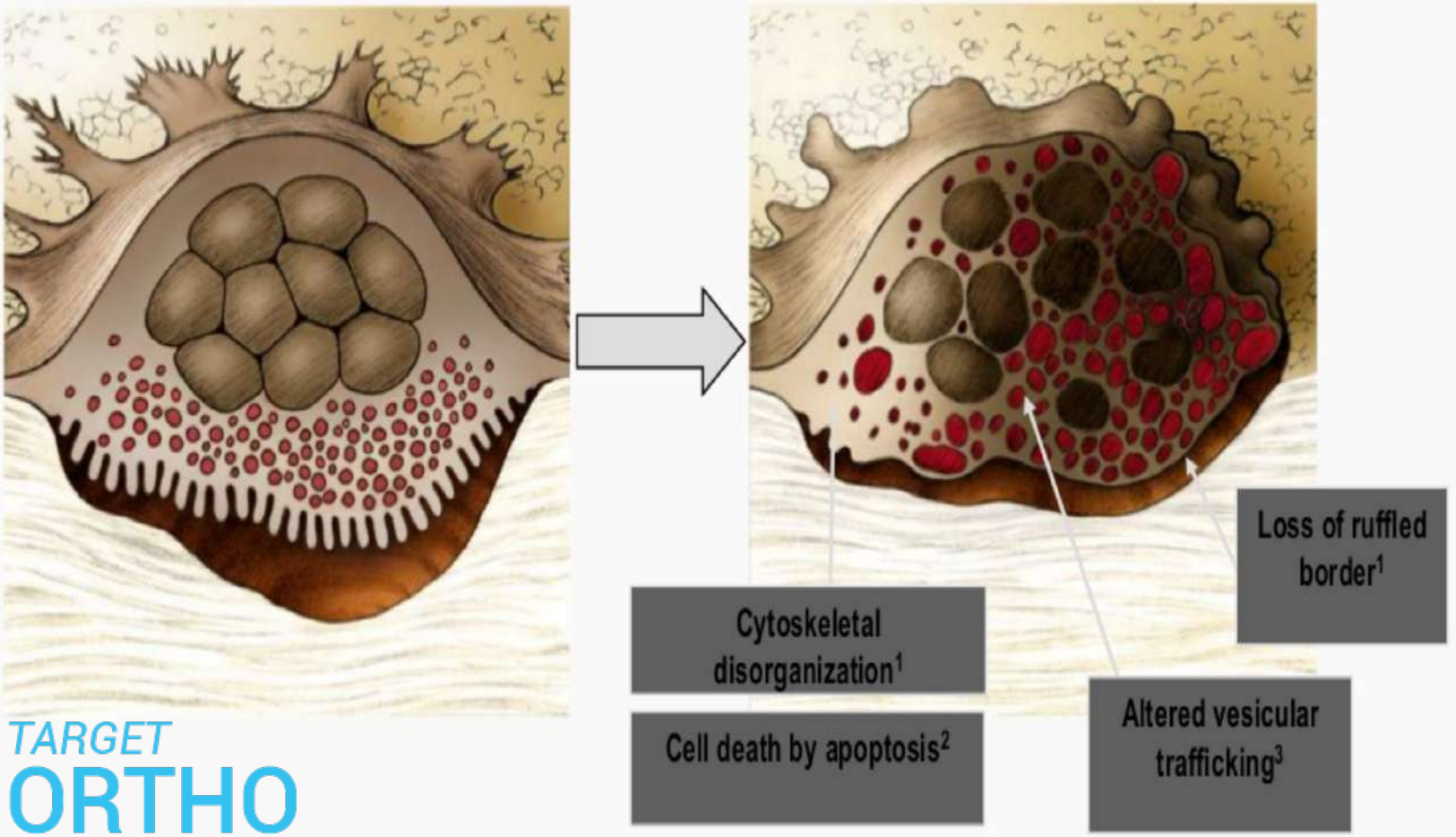
- ***Antiresorptive Agents***
- Hormone/estrogen therapy
- Selective estrogen receptor modulators (SERMS)
- Specific for the treatment of osteoporosis (bisphosphonates, denosumab, and calcitonin)
- ***Anabolic Agents***
- Teriparatide
- Abaloparatide and Romosozumab

Antiresorptive Agents

Bisphosphonates

- Bisphosphonates specifically **impair osteoclast function** and **reduce osteoclast number, by inducing apoptosis.**
- Alendronate, risedronate, ibandronate, and zoledronic acid - **postmenopausal osteoporosis**
- Alendronate, risedronate, and zoledronic acid - **steroid-induced osteoporosis**
- risedronate and zoledronic acid **for prevention of steroid-induced osteoporosis**
- Alendronate, risedronate, and zoledronic acid for treatment of **osteoporosis in men.**

Effects of Bisphosphonates on Osteoclast Function



- *Alendronate*
- Decreases bone turnover
- Increases bone mass in the spine by up to 8% and by 6% in the hip
- 70 mg weekly or 10 mg daily
- Reduced vertebral fracture risk by about 50%,
- Multiple vertebral fractures by up to 90%,
- Hip fractures by up to 50%.

- *Risedronate* also reduces bone turnover and increases bone mass
-
- 40–50% reduction in vertebral fracture ,a 40% reduction in clinical non-spine fractures

- 35 mg of risedronate once weekly is therapeutically equivalent to 5 mg/d.

- Ibandronate (2.5 mg/d)(150mg/month) reduce vertebral fracture risk by ~40% but
  with no overall effect on non-vertebral fractures

- *Zoledronic acid* is a potent bisphosphonate with a unique administration regimen (5 mg by 15 min IV infusion annually)
-
- zoledronic acid reduced the risk of vertebral fractures by 70%, nonvertebral fractures by 25%, and hip fractures by 40%

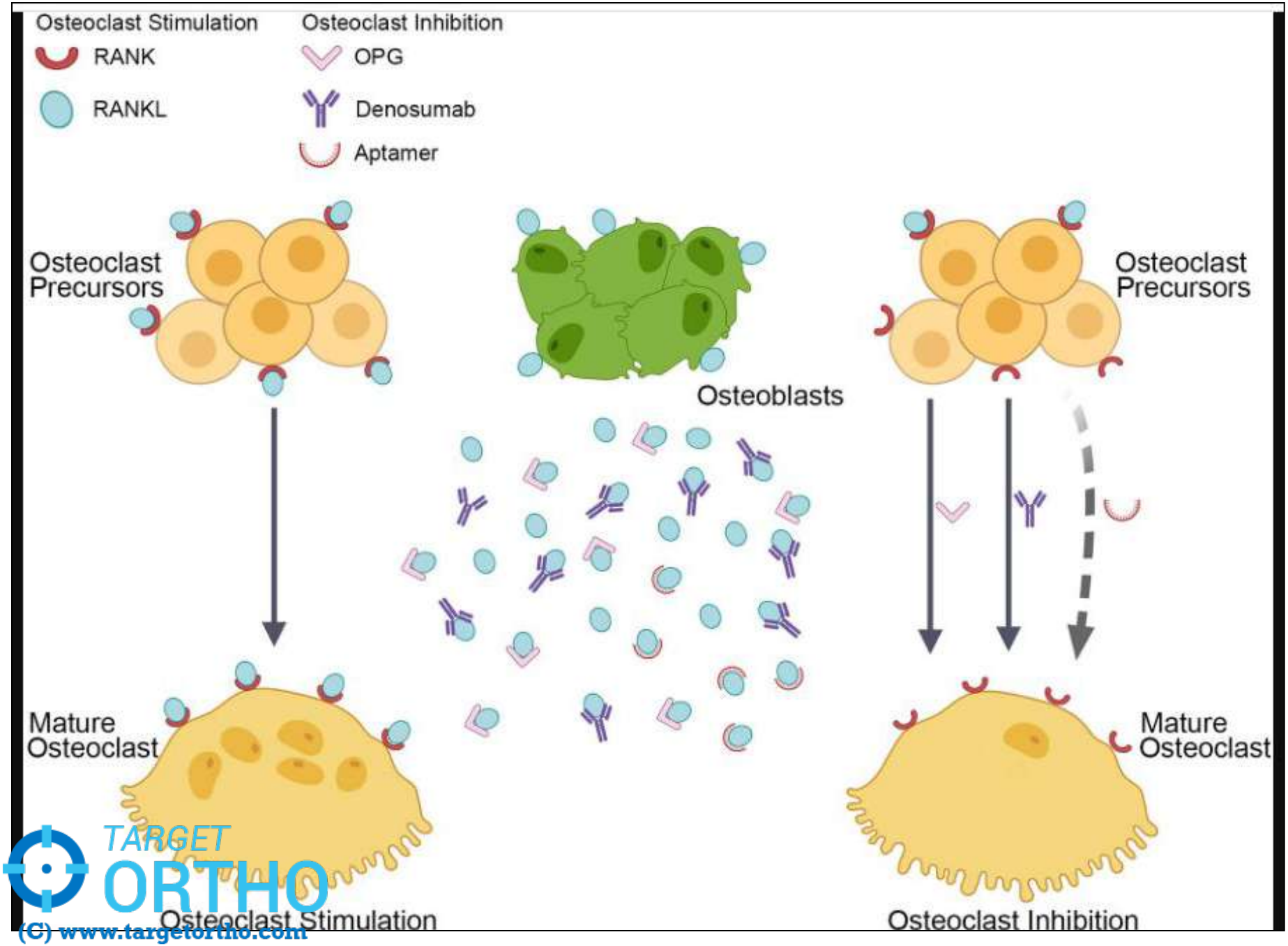
Common Bisphosphonate Adverse Events

- **Musculoskeletal and joint pains**
-
- **Renal toxicity** and bisphosphonates are contraindicated in those with estimated GFR <30–35 mL/min
- **Hypocalcemia** can occur
- Osteonecrosis of the jaw (ONJ)
-
- Atypical femoral fracture - unusual fractures that occur in the subtrochanteric femoral region or across the femoral shaft distal to the lesser trochanter. (preceded by pain in the lateral thigh or groin, that can be present for weeks, months or even years before the fracture.)

	Alendronate	*Zoledronc acid*	Ibandronate	*Risedronate*
REDUCED VERTIBRAL FRACTURE BY	50%	70%	~40%	40–50%
HIP FRACTURE BY	50%.	40%	no overall effect	40%

Calcitonin

- Approved by the FDA for Paget's disease, hypercalcemia, and osteoporosis in women >5 years past menopause.
- Calcitonin suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor
- A nasal spray containing calcitonin (200 IU/d) for treatment of osteoporosis
- Injectable calcitonin produces small increments in bone mass of the lumbar spine



Denosumab

- Human monoclonal antibody to RANKL
- Denosumab binds to RANKL, **inhibiting its ability to initiate formation of mature osteoclasts from osteoclast precursors** and to bring mature osteoclasts to the bone surface and initiate bone resorption.
- Plays a role in reducing the survival of the osteoclast

Denosumab

- **given twice a year 60 mg s/c**
- shown to increase BMD in the spine, hip, and forearm
- reduce vertebral, hip, and nonvertebral fractures by 70, 40, and 20%, respectively

❖ **<u>Denosumab is approved for the treatment of</u>**

- ***osteoporosis in men*** at high risk for fracture,
-
- women with breast cancer on **aromatase inhibitors**
-
- men with prostate cancer on **androgen deprivation treatment**

Denosumab

- Increase the risk **of ONJ and atypical femur #**
- Cause hypersensitivity reactions, hypocalcemia and skin reactions including dermatitis, rash, and eczema

❖ Discontinued, there is a rebound increase in bone turnover and acceleration of bone loss

rapid increase in the risk of fracture,

particularly vertebral fracture

Drug holiday

- A drug “holiday” is not recommended with **denosumab**.
- For oral bisphosphonates “ bisphosphonate holiday ” after 5 ys

  For iv bp holiday after 3 years

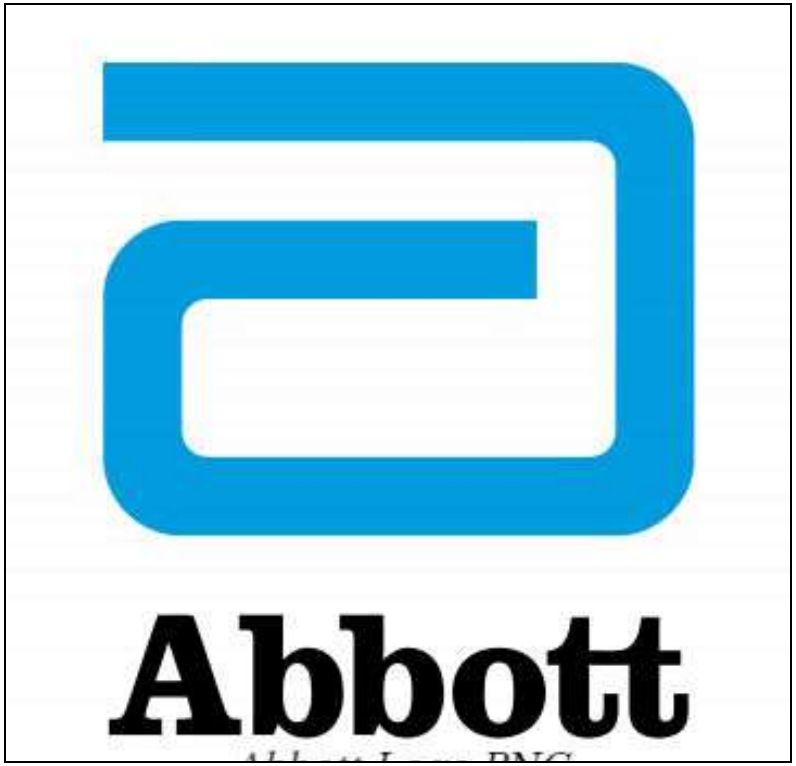
	Alendronate	*Zoledronc acid*	*Risedronate*
HOLIDAYS	3 – 5 YRS	3 – 6 YS	1 – 2 YRS

- Teriparatide may be used in this time

In CKD ?

- Risk is high
- Bone biopsy prior to treatment
- To differtiate bone turnover rates
- Serum PTH & ALP levels as proxy markers
- **Denozumab s**afe coz not excreted renally

Denaxa



SERMs (*Selective estrogen receptor modulators)*

- **raloxifene**
  - for the prevention and treatment of osteoporosis as well as the prevention of breast cancer

- **tamoxifen** for prevention **and treatment of breast** cancer
- **Bazedoxifene**
  - in combination with conjugated estrogen for **treatment of menopausal symptoms and prevention of bone loss**

Mode of Action of SERMs

- All SERMs bind to the ER
- In contrast to tamoxifen, raloxifene is not associated with an increase in the risk of uterine cancer or benign uterine disease.

Estrogens

- reduce bone turnover, prevent bone loss, and induce small increases in bone mass of the spine, hip, and total body
- 50% reduction, on average, of osteoporosis related fractures, including hip fractures.
- estrogen effects on bone resorption are mediated indirectly through paracrine factors produced by osteoblasts.
- (1) increasing OPG production by osteoblasts
- (2) Increasing IGF-I and TGF-β
- (3) suppressing IL-1 (α and β), IL-6, TNF-α, and osteocalcin synthesis.

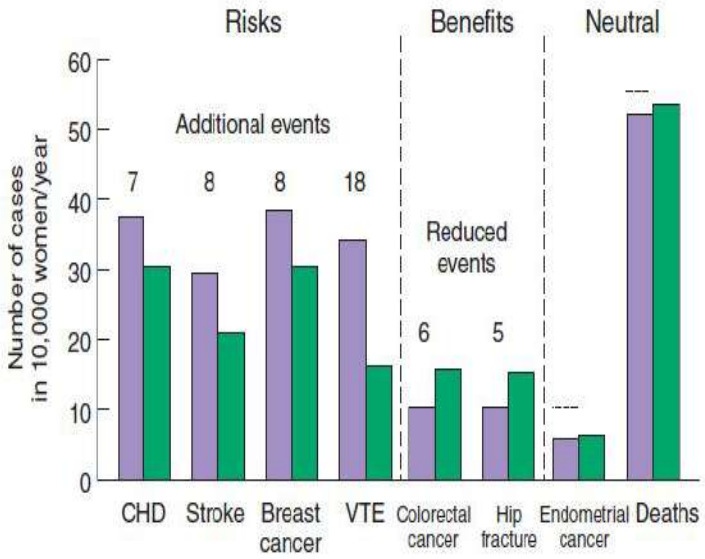


FIGURE 404-8 Effects of hormone therapy on event rates: green, placebo; purple, estrogen and progestin. CHD, coronary heart disease; VTE, venous thromboembolic events. *(Adapted from Women's Health Initiative. WHI HRT Update.*

- relative risks :
- **increased risk of fatal and nonfatal myocardial infarction by ~29%**
- a 40% increase in **stroke,** a 100% increase **in venous thromboembolic disease**, and a 26% increase in risk of **breast cancer**

Anabolic Agents

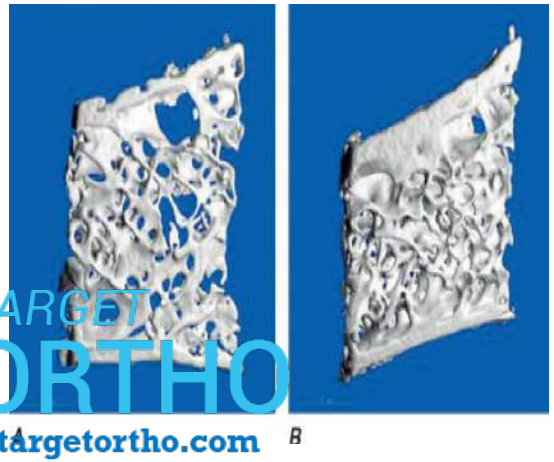
Parathyroid Hormone

- responsible for calcium homeostasis
- chronic elevation of PTH
- associated with bone loss (particularly cortical bone),

hyperparathyroidism is associated with maintenance of trabecular bone mass, but loss of cortical bone

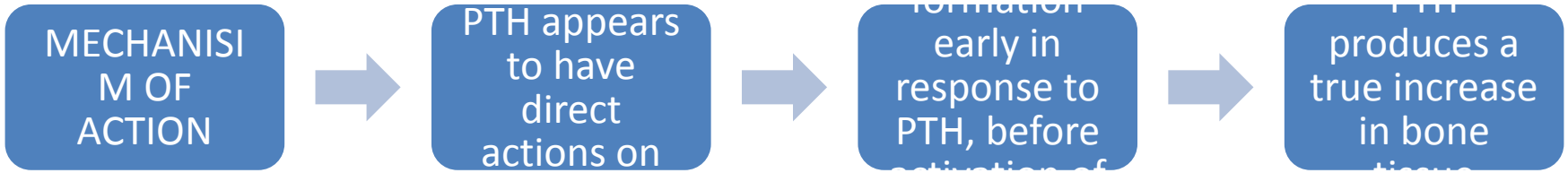
PTH analogues could augment trabecular BMD

increase bone mass and reduce fracture occurrence



Teriparatide

(1–34)PTH



- Teriparatide produces **rapid increases in bone formation** and then bone remodeling overall, resulting in increases in bone mass
- **improvements in microarchitecture**, including cancellous connectivity and cortical width
- **Side effects of teriparatide are generally mild** and can include muscle pain, weakness, dizziness, headache, and nausea.
- **Rare cases of osteosarcoma have been described**

Abaloparatide

- A synthetic analogue of human PTH-related peptide (PTHrP)
- Binds the PTH Type 1 Receptor.
- **PRODUCE MORE bone formation stimulus but lesser bone resorption stimulus**
- Vertebral fracture incidence was reduced by 86% with abaloparatide and 80% with teriparatide

Decision makings

- Very high risk cases
- Teriparatide – in cases of vertebral fractures for 2 yrs followed by annual zoledronate or denozumab twice a year
- Zoledronate – hip fractures x minimum 6yrs
- Denozumab – hip & vertebral x 7 yrs f/b zoledronate

- Moderate to low risk
- Zoledronate
- Alendronate
- Risedronate
- denozumab

- Moderate to low – with prevention of vertebral only
- Teriparatide
- Denozumab
- Raloxifene
- Ibandronate
- Alendronate
- Risedronate

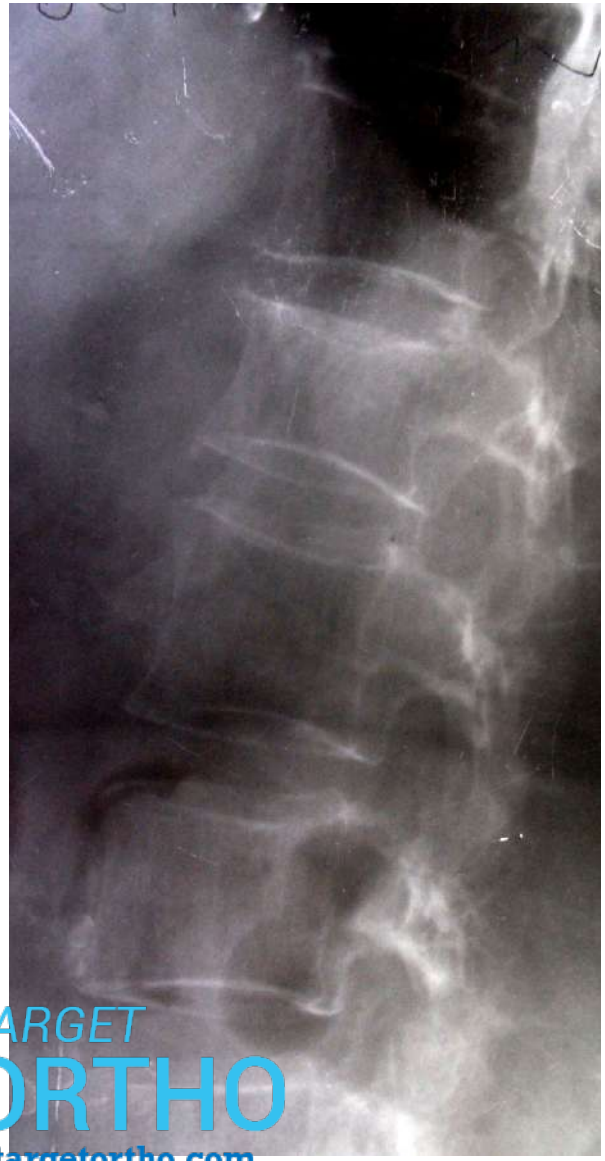
In CKD ?

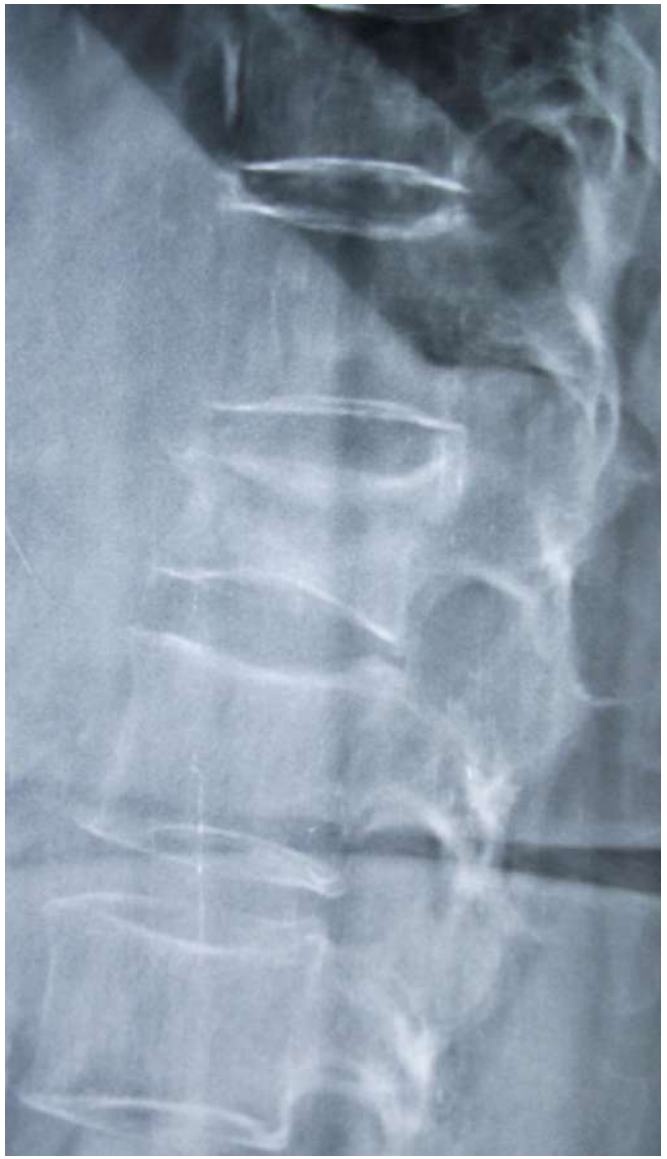
- Risk is high
- Bone biopsy prior to treatment
- To differtiate bone turnover rates
- Serum PTH & ALP levels as proxy markers
- **Denozumab s**afe coz not excreted renally

Monitoring of therapy

- Both DXA & BTM
- DXA at baseline
- Repeated after 1-2 years of initiation
- BTM after 6 mnoths of initiation

Osteoporotic compression fractures





Osteoporotic compression fractures