

# Osteoporosis

Gary

Key points  
Epidemiology Clinical  
Pathology  
Men

## Key points

→ Osteoporosis: Bone density → ↓  
Microarchitecture → deterioration } → ↓ Bone strength → ↑ fracture risk

## → Risk factors for osteoporotic fracture

Age ↑

Weight ↓

Family hx of hip fragility fracture

GC use

Inability to move from chair

Frequent falls

♂: 2/3 → secondary cause found

## FRAX

10y fracture risk for:

- hip

- other major osteoporotic fracture sites

if ↑ → Trt

## → Postmenopausal / Age related:

↑ resorption } → net bone loss  
↓ formation

→ Estrogen deficiency → ↑↑ Turnover  
Trt

### Anti-resorptive

Estrogen

Raloxifene

Biphosphonate

alendronate

risedronate

Zoledronic acid

Ibandronate

Denosumab

-ronate

alen

use

zole

iban

### Anabolic agents

Recombinant human

parathyroid hormone

1-34

Trt anti-resorptive } → ↓ incidence of vertebral fracture  
anabolic

\* Bisphosphate treatment, when can it be discontinued?

3-5 years

no  $f\#$  sustained

~~FRA~~  
Risk factors for  $f\#$  are low

discontinue and observe

\* PTH

Anabolic

↑ osteoblasts maturation and life span.

↑ Trabecular bone mass

↑ Cortical thickness

↓ overall risk for  $f\#$



Pizza  
Tacos  
Hamburger



full course of PTH  $\xrightarrow{\text{then}}$  anti-resorptive therapy

\* GCT

GCT  $\left\{ \begin{array}{l} \text{Osteoclast activity } \uparrow \\ \text{Osteoblast activity } \downarrow \end{array} \right\}$  — bone loss: most severe in the 1<sup>st</sup> 6 months of therapy

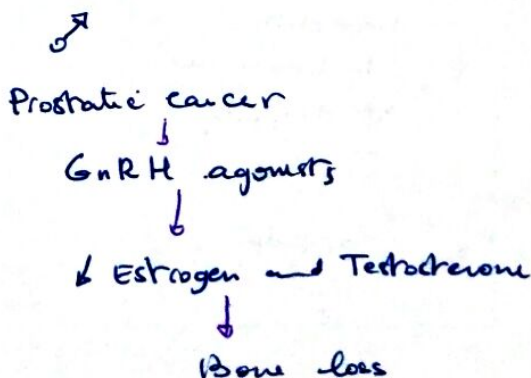
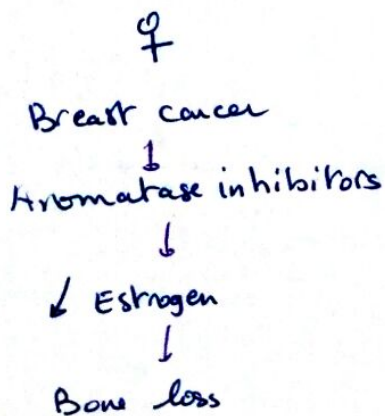
Tx bisphosphate  $\rightarrow$  prevent  $f\#$

hPTH(1-34)  $\rightarrow$  reverse GCT induced osteoporosis  $\rightarrow$  ↓ incident  $f\#$

\* Aromatase inhibitors

Aromatase inhibitors  $\rightarrow$  ↓ serum Estrogen  $\rightarrow$  rapid bone loss in post-menopausal  $\#$  undergoing adjuvant breast cancer therapy.

\* GnRH agonists  $\rightarrow$  ↓ serum Testosterone and Estrogen  $\rightarrow$  bone loss in men treated for prostatic cancer



# Osteoporosis

Bone

density ↓

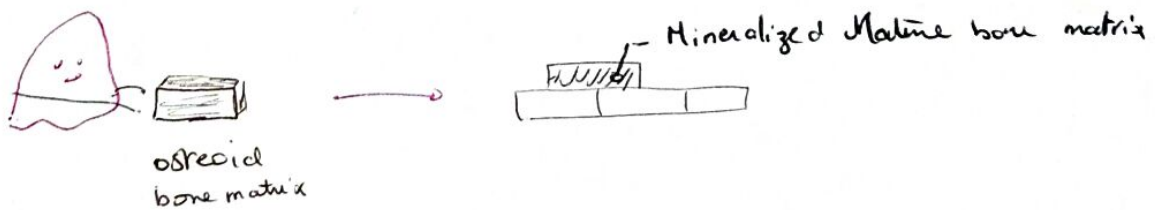
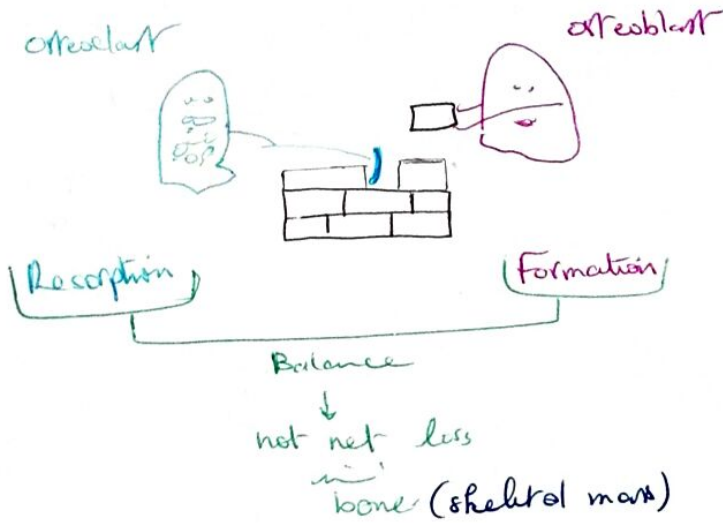
microarchitecture, deteriorated

## Bone

Organic matrix: collagen - non collagenous proteins

Inorganic mineral component: calcium and phosphate (hydroxyapatite form)

## Bone Turnover



## Bone

Cortical (80%)

Stronger

Appendicular skeleton:

Femoral neck

Trabecular (20%)

more active metabolically

Spine

Epiphysis

Pelvis

## Osteoporosis

↓ bone strength

mineral?

↓ bone mass

organic?

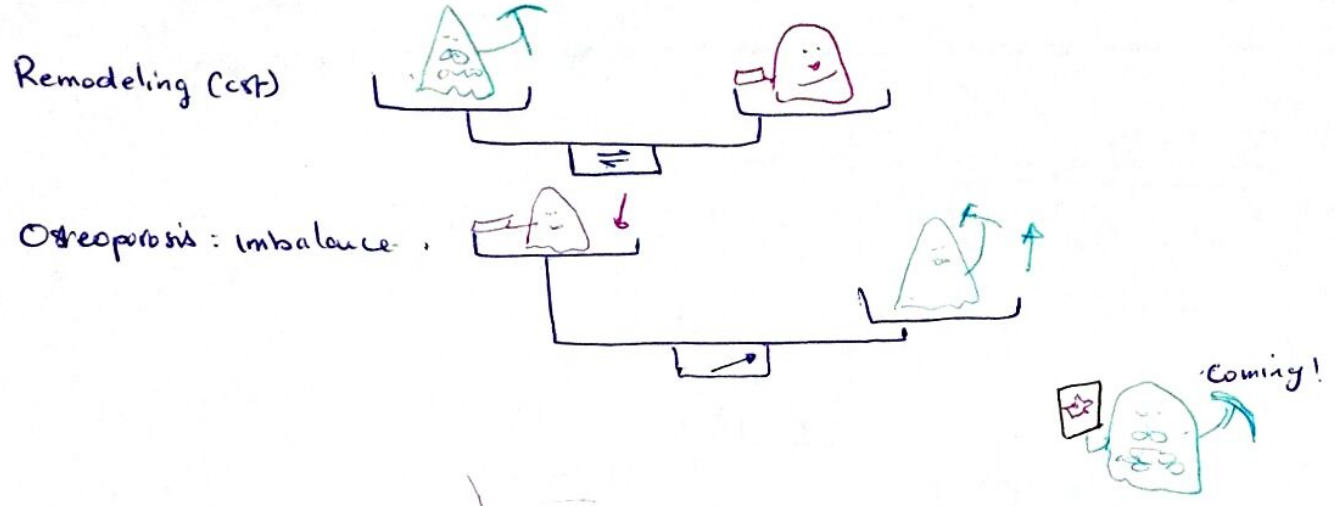
## Osteomalacia

↓ bone Mineralization of bone matrix

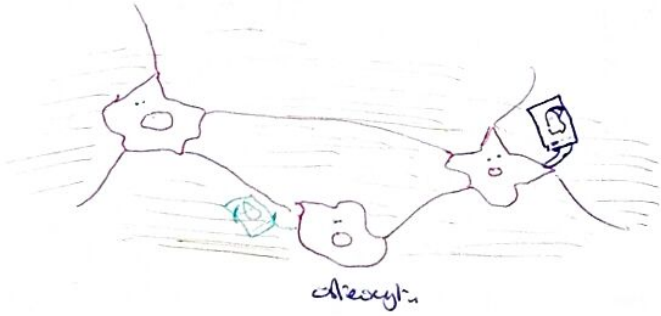
Pathophysiology - menopause  
 - age related bone loss

Bone constantly undergoing remodeling

Osteoclasts → resorption areas  
 ↑  
 osteoblasts → replace them by new bone  
 Osteoporosis → imbalance



osteoblast ≠

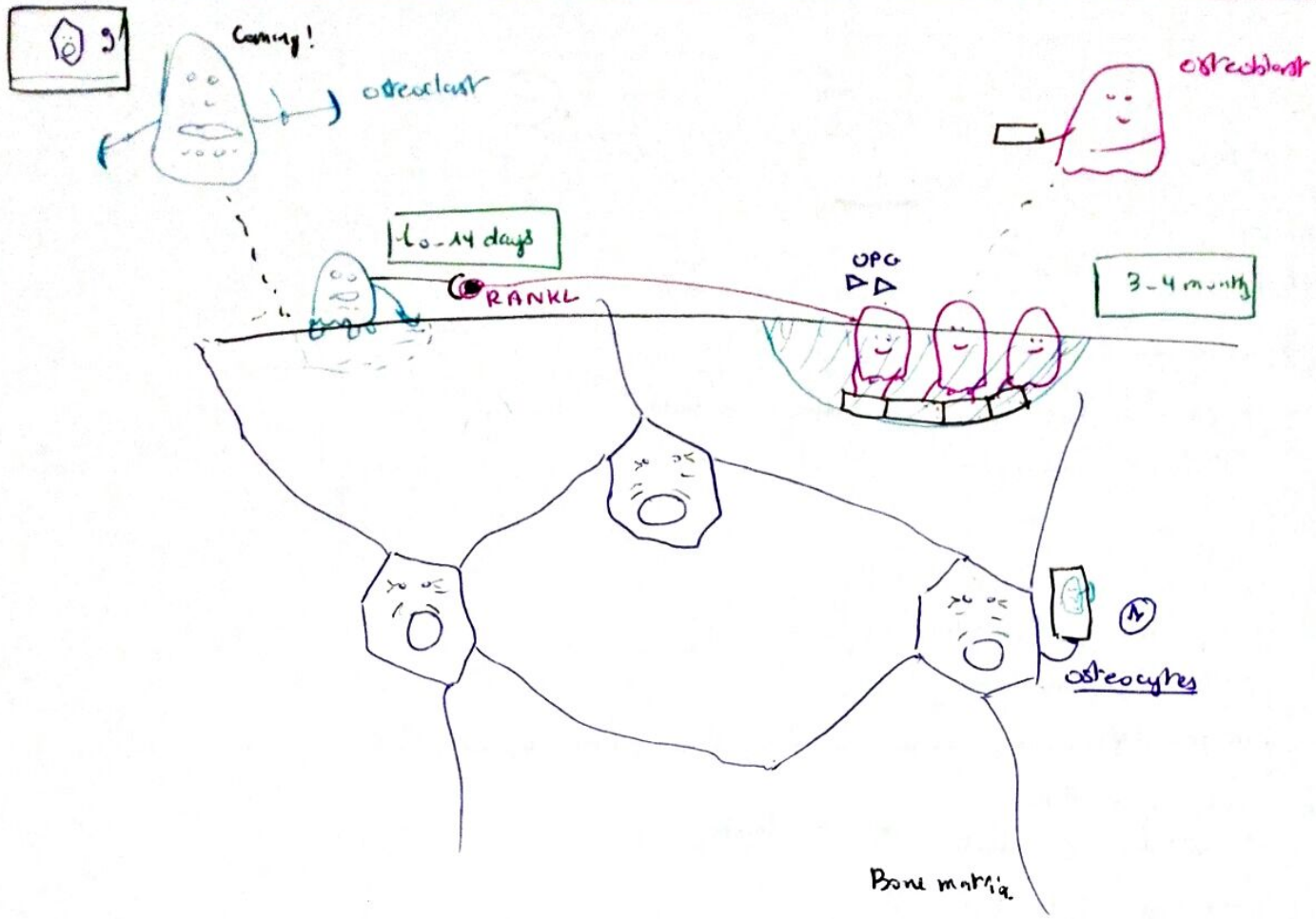


Osteoblasts → osteocytes

- within bone matrix
- connected to each other
- to the bone surface.
- produce chemicals attracting osteoclasts

Osteoclasts  
 ↓  
 e. : hematopoietic stem cell  
 ↓  
 colony forming unit - granulocyte - monocyte  
 ↓  
 osteoclasts

osteoblasts  
 e. : Bone marrow mesenchymal stromal cells



Osteoclasts  
 Hematopoietic stem cell  
 ↓  
 CFU: monocyte-granulocytes  
 ↓  
 osteoblast

Osteoblast  
 bone marrow mesenchymal cells

Osteocyte  
 osteoblast

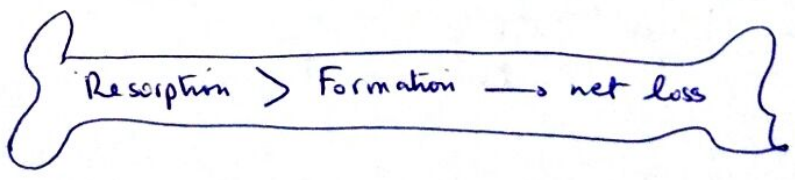
Osteocytes: → chemical mediators → attract osteoclasts

Osteoclasts: attach to bone surface  
 bone resorption  
 10-14 days

Osteoblasts: attach to the resorbed bone  
 produce osteoid which will be mineralized  
 bone formation - 3-4 months

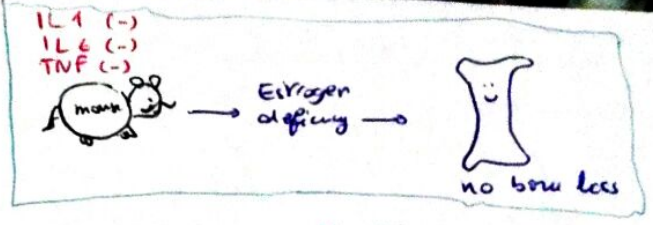
Factors ———— [ ↑ number / ↑ activity ] of osteoclasts → ↑ resorption: uncoupled turnover

- Metabolic changes
- estrogen deficiency
  - immobilization
  - metabolic acidosis
  - ↑PTH
  - inflammatory diseases



Local bone factors

- IGF<sub>1</sub>
  - IL (1, 6, 11)
  - TNF
  - RANKL
  - TGF- $\beta$
- }  $\rightarrow$   $\oplus$  osteoclasts



Inflammatory arthritis

Primary osteoporosis

- low peak bone mass as a young adult
- rapid bone loss during menopause

Age related bone loss factors:

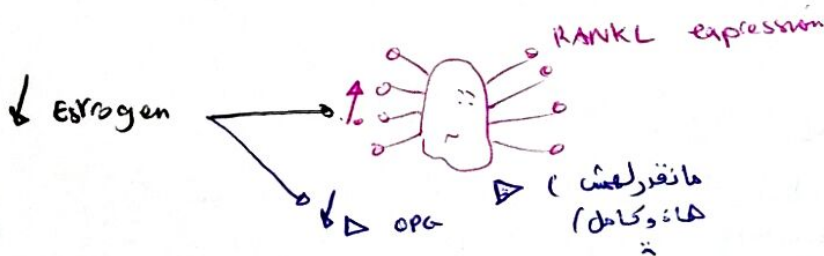
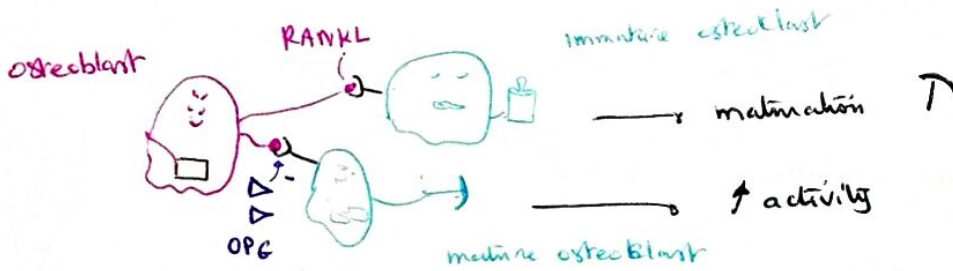
- impaired Ca<sup>2+</sup> absorption
- Compensatory  $\uparrow$  in PTH
- resorption > formation
- estrogen deficiency  $\rightarrow$  release of cytokines (RANKL, IL1, IL6, TNF)

- $\rightarrow$  recruitment  $\uparrow$  N
- stimulation  $\oplus$  activity of osteoclasts
- with age:  $\uparrow$  IL 6 levels

IL1, TNF  $\rightarrow$  osteoblasts stromal cells  $\rightarrow$  IL6 production

Osteoprotegerin and RANKL

Osteoblasts produce: - OPG =  $\downarrow$  RANKL production and activity  
- RANKL



anti RANKL mab  $\rightarrow$  prevent estrogen deficiency bone loss

Estrogen  $\downarrow$       osteoblast RANKL  $\uparrow$       OPG  $\downarrow$       osteoclast  $\uparrow$

## Genetic Nutritional Lifestyle factors

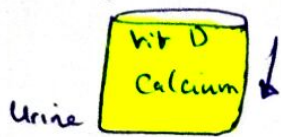
White and Asians

↑ risk for osteoporosis

→ African-Americans

African-Americans

↓ risk for osteoporosis  
bone density ↑



PTH [ ] ↑ levels  
resistance to its skeletal effects

Genetic factors → 80% of bone density variance

Family hx of fragility fr → risk factor for fragility fr

## Secondary osteoporosis

Most common GCT therapy

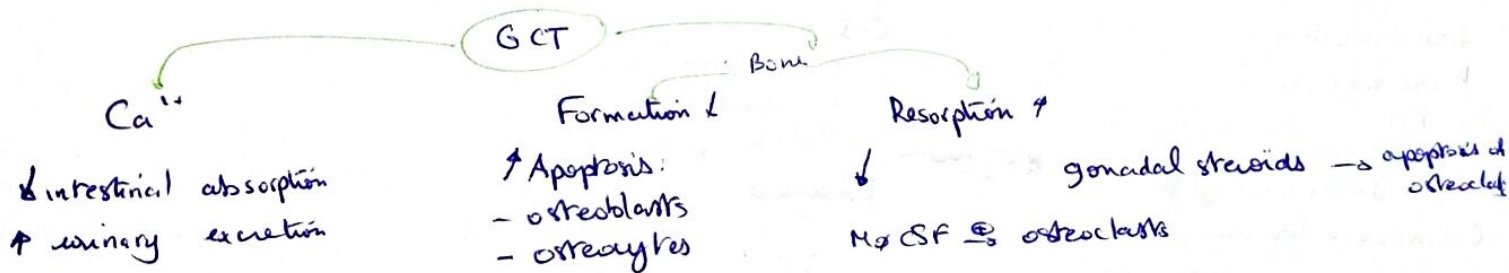
≠ Mechanisms:

Intestinal calcium absorption impairment

Urinary calcium excretion ↑

↓ bone formation: dose dependent ↑ of osteocytes osteoblasts apoptosis

↑ bone resorption /   
 ↳ M $\alpha$  CSF → osteoclasts  
 ↳ ↓ endogenous gonadal steroids



GCT → early +1 - dramatic loss of trabecular bone  
 ↳ less effects on cortical bone

Hyperthyroidism  
 Supraphysiologic therapy (TH) } → accelerated bone turnover → ↓ bone mass  
 ↳ white (TSH suppressed)  
 ↳ TH is normal [ ]

Hypogonadal states: athletic amenorrhea, anorexia nervosa and other GnRH agonists... } → bone loss.

Woman + anorexia nervosa

↓ IGF-1  
↓ adrenal androgen dehydroepiandrosterone } → osteoporosis in dupl.

## Osteoporosis in men

♂ Fracture risk

a adolescent, young adult

long bone

> 70

hip  
spine

old man + 10 years = menopausal woman

♂ hip fracture death within the 1st year  
permanent disability risk > ♀

Secondary causes: hypogonadism

gonadal failure ↓ with age

androgen deprivation therapy for prostatic cancer

estrogen and testosterone roles

♂ 2<sup>nd</sup> causes - hypogonadism  
- alcoholism  
- GI disorder hepatic malabsorption

## Secondary causes

Immobilization

Bone marrow:

MH

Leukemia

Systemic mastocytosis

Connective tissue:

Osteogenesis imperfecta

Homocysteinuria

Ehler Danlos Syd

Rheumatologic:

RA

AS

SLE

GI:

Gastrectomy

Celiac disease

Malabsorption

Endocrine:

Glucocorticoid ↑

TH ↑

PTH ↑

Hypercalciuria

Hypogonadism

Renal insufficiency

Chronic respiratory disease

Medications:

GCT

Aromatase inhibitors

GnRH and Cyclophosphamide

Cyclosporine

Heparin

MTX

Anti convulsant

Pre-menopausal Tamoxifen

Alcohol ↑↑↑



# Osteoporosis

## Secrets

o Fragility f# risk factors:

↓ bone mass

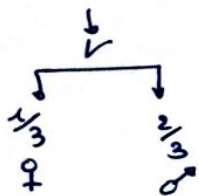
previous fragility f#

↑ Age

CTC

propensity for falling

o Disorder → 2<sup>nd</sup> osteoporosis



⇒ Workup to identify them

[ Hx  
PE  
Labs (cost-effective)

o GCT → ↑ risk of osteoporotic f#

o GCT →  $\left\{ \begin{array}{l} \downarrow \text{formation} \\ \uparrow \text{resorption} \end{array} \right\} \Rightarrow \text{rapid bone loss}$

### 1. Osteoporosis

Bone disorder → ↓ bone strength

bone strength determined by [ Bone mass  
Bone quality

↓  
fragility f#

Dg. fragility f#  
BMD measurement

### 2. Fragility f#

f# occurring - spontaneously

- after minimal trauma: falling from standing height or less

Most characteristic

vertebral

hip

distal radius (Colles f#)

Osteoporosis → all types of f# are possible.

### 3. Complications of osteoporotic f#

Vertebral f#

$\left\{ \begin{array}{l} \downarrow \text{height} \\ \text{anterior kyphosis (dowager's hump)} \\ \downarrow \text{pulmonary function (each f#} \rightarrow \downarrow \text{FVC by 9\%)} \\ \uparrow \text{mortality rate} \end{array} \right.$

Vertebral f#  $\left\{ \begin{array}{l} \uparrow 2/3 \rightarrow \text{Asx} \rightarrow \text{cpc.} \\ \downarrow 1/3 \rightarrow \text{Sx} \end{array} \right.$

Hip f# disability  
mortality

#### 4. Risk factors of osteoporotic fractures

##### Osteoporosis

↓ BMD

↑ Age

Previous fragility fr

Frequent falls

Corticosteroids use.

#### 5. BMD indications:

Age: ♀ ≥ 65 ; ♂ ≥ 70

Estrogen deficiency + ⊕ osteoporosis factor

Vertebral  $\left\{ \begin{array}{l} \text{deformity} \\ \text{fr} \\ \text{osteopenia} \end{array} \right. \xrightarrow{\text{x Ray}}$

GCT therapy: (Prednisone ≥ 5mg / d for ≥ 3 months)

#### 6. How BMD is measured

DEXA: most accurate.

Dual Energy X ray Absorptiometry

DEXA measurements  $\left\{ \begin{array}{l} \text{Central} \rightarrow \text{Spine, hip} \rightarrow \text{best predictor for fr with} \\ \text{Peripheral} \rightarrow \text{heel, radius, hand} \rightarrow \text{more available but less} \\ \hspace{15em} \text{accurate.} \end{array} \right.$

#### 7. How to read a BMD report

T-score / young normal subject  $\rightarrow$  osteoporosis

Z-score / age matched normal patient  $\rightarrow$  secondary cause other than  
- age  
- menopause

Absolute BMD  $\rightarrow$  [g/cm<sup>2</sup>] . follow up ↓

#### 8. How is the Dx made?

1.) Fragility fr

· fragility fr  
· > 50y  $\rightarrow$  T. score  $\leq -2,5$   
· < 50y  $\rightarrow$  Z. score  $\leq -2,0$

2.) 50y patient  $\rightarrow$  BMD T. score at the lowest skeletal site.



osteoporosis: BMD T score  $\leq -2,5$

3) Premenopausal ♀ }  $\rightarrow$  BMD Z. score at the lowest skeletal site.  
    < 50 y ♂ }

BMD Z score  $\leq -2,0$

9)

T. score  $\downarrow$   $\rightarrow$  bone loss  $\uparrow$   $\rightarrow$  fracture risk  $\uparrow$

At the same T. score an older patient is more likely to suffer from - fracture

### 10) Major risk factors for osteoporosis

#### Non modifiable

- Age  $\uparrow$
- Race (white, asian)
- Female gender
- Early menopause
- Slender built
- ⊕ family Hx
- Chin fragility fracture

#### Modifiable

- Calcium intake  $\downarrow$
- Vit D intake  $\downarrow$
- Estrogen deficiency
- Sedentary lifestyle
- Cigarette's smoking
- Alcohol excess ( $> 2$  drinks/d)
- Caffeine excess ( $> 2$  servings/d)

Age  $\uparrow$

Estrogen  $\downarrow$



Cigarette  
Caffeine  
alcohol

Blonde

Female

Calcium  $\downarrow$

Girl, premenopausal

D vit  $\downarrow$

Hx Hip fragility fracture

11) Conditions that must be excluded.

12) Cost effective evaluation to rule out underlying condition

Ca<sup>2+</sup> (Albumin), phosphorus, creatinine, CO<sub>2</sub>

Alkaline phosphatase

25-hydroxy (OH) vit D

Testosterone (♂)

TSH - clinical

Celiac disease Ab testing (white + [ $\downarrow$  25-OH vit D])

Urine 24h: Ca<sup>2+</sup>, sodium, creatinine

SPEP if  $> 50$  + abnormal CBC

$\frac{1}{3}$  ♀ }  $\rightarrow$  an abnormality will be found.  
 $\frac{2}{3}$  ♂

Z. score  $\rightarrow$   $\downarrow$   $\rightarrow$  secondary osteoporosis

13) How to determine whether the patient had a previous vertebral f#

Back pain  
Tenderness

but  $\frac{1}{3}$  vertebral f# are asymptomatic

Height loss

Dorsal kyphosis

→ Lateral spine films

→ DXA

14) Risk factors for frequent falls

Sedative use

Cognitive impairment

Visual impairment

Frailty

Lower extremity disability

Obstacle to the ambulation in the home

Most predictive

△ Risk factors for:

Osteoporosis

ABCDEFGHIH 

Falls

Sedatives

Cognitive

Visual

Frailty

LE disability

Obstacle to ambulation

Fractures in osteoporosis

CTC use

Age ↑

frequent falls

↓BMD

Previous fragility f#

Age ↑

BMD ↓

CTC use

E ↓

Falls frequent

Fragility f#

16) Osteoporosis in men

Same Dg criteria ♂ and ♀

♂:  $\frac{2}{3}$  have an identifiable secondary cause most often:

- alcohol abuse

- GCT use

- hypogonadism

↳ GnRH analog in prostate cancer

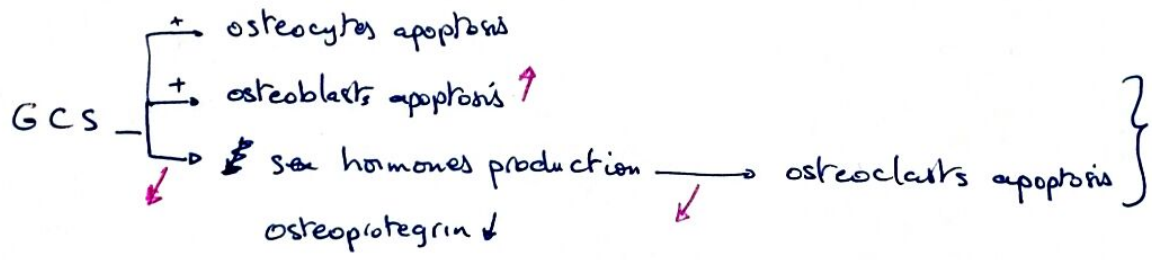
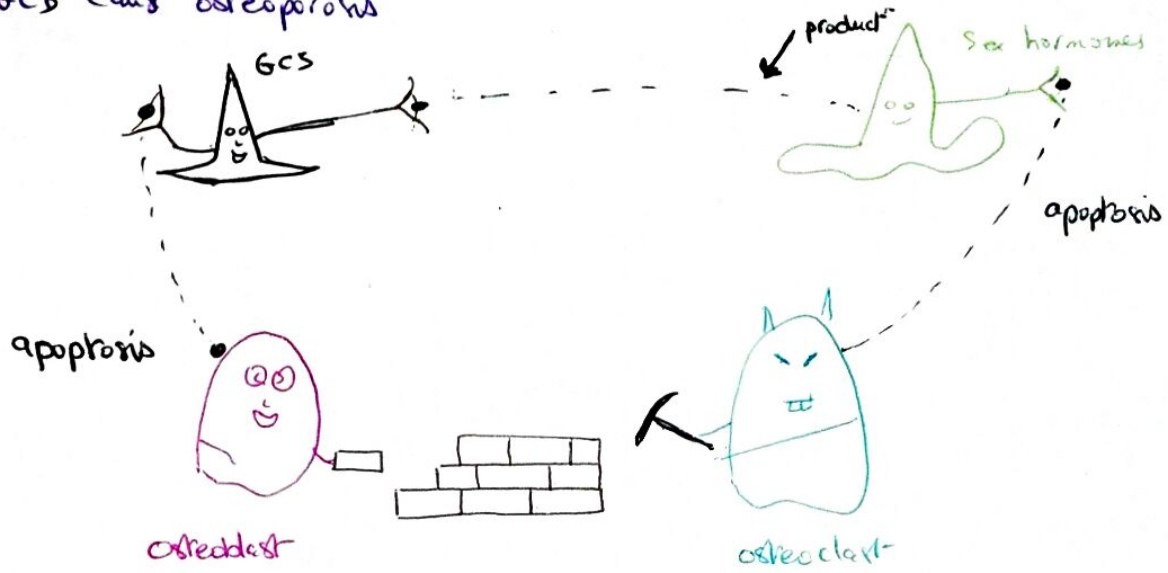
Tx: the same

but also: Testosterone replacement therapy if hypogonadism

17. When pharmacological therapy should be initiated?

- Hx of vertebral or hip fragility f#
- T-score < -2.5
- Drug naïve; >40y with osteopenia (-2.5, -1) and 10y f# risk / FRAX
  - ≥ 3% → hip f#
  - ≥ 20% → other major fragility f#.

18. How GCS cause osteoporosis



- ⊕ Osteoblasts apoptosis
- ↓ sex hormones
- ↓ osteoprotegrins } which ⊖ resorption
- ⊕ osteocytes apoptosis