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Drug-induced Osteoporosis

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Drug Induced osteoporosis

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- 2020 Bone and Mineral Symposium

Objectives

- Drugs that cause bone loss or osteoporosis
- Pathophysiology
- Prevention
- Treatment

Drugs that cause osteoporosis

- Glucocorticoids - Prednisone, Methylprednisolone
- Hormone blockers - Aromatase inhibitors (letrozole, anastrozole, exemestane), GnRh agonists, Anti-androgen (5 alfa reductase inhibitors and androgen receptor blockers), Progesterone only contraception.
- Anticonvulsants - enzyme inducers that breakdown vitamin D (phenytoin, phenobarbital, carbamazepine, primidone), Levetiracetam, Drugs that cause chronic metabolic acidosis (Topiramate, Zonisamide)
- Antidiabetic Meds - Thiazolidinediones and SGLT-2 inhibitors
- Thyroid hormone excess.
- PPIs and SSRIs

Drugs that cause osteoporosis

- Diuretics - Furosemide, caffeine (urine calcium loss) Acetazolamide (metabolic acidosis)
- Anticoagulants – Heparin, Warfarin
- Misc - Lithium increases PTH and bone turnover.
- Cyclosporine and Tacrolimus – cause increased bone turnover and bone loss in animals and transplant patients.
- High dose methotrexate, such as used in oncology may increase risk of OP - imbalance of bone resorption and formation.

- *US Pharm*. 2006;12:HS3-HS6.
- *Ther Adv Muskuloskel Dis*: 2014, Vol. 6(5) 185 - 202

- Steroid Induced Osteoporosis

Steroid induced osteoporosis - General

- Glucocorticoids are widely used and are effective in treating many pulmonary, rheumatologic, autoimmune gastrointestinal, dermatologic conditions and in organ transplantation. Used in 0.5 - 1% of general population.

- Cause osteoporosis in a dose and time dependent manner. The risk of bone loss is greatest within the first 6 to 12 months of long-term therapy and fractures can occur in as early as 6 months.

- An estimated 30% to 50% of patients taking systemic long-term steroids will eventually experience a fracture.

Steroid Osteoporosis - Incidence

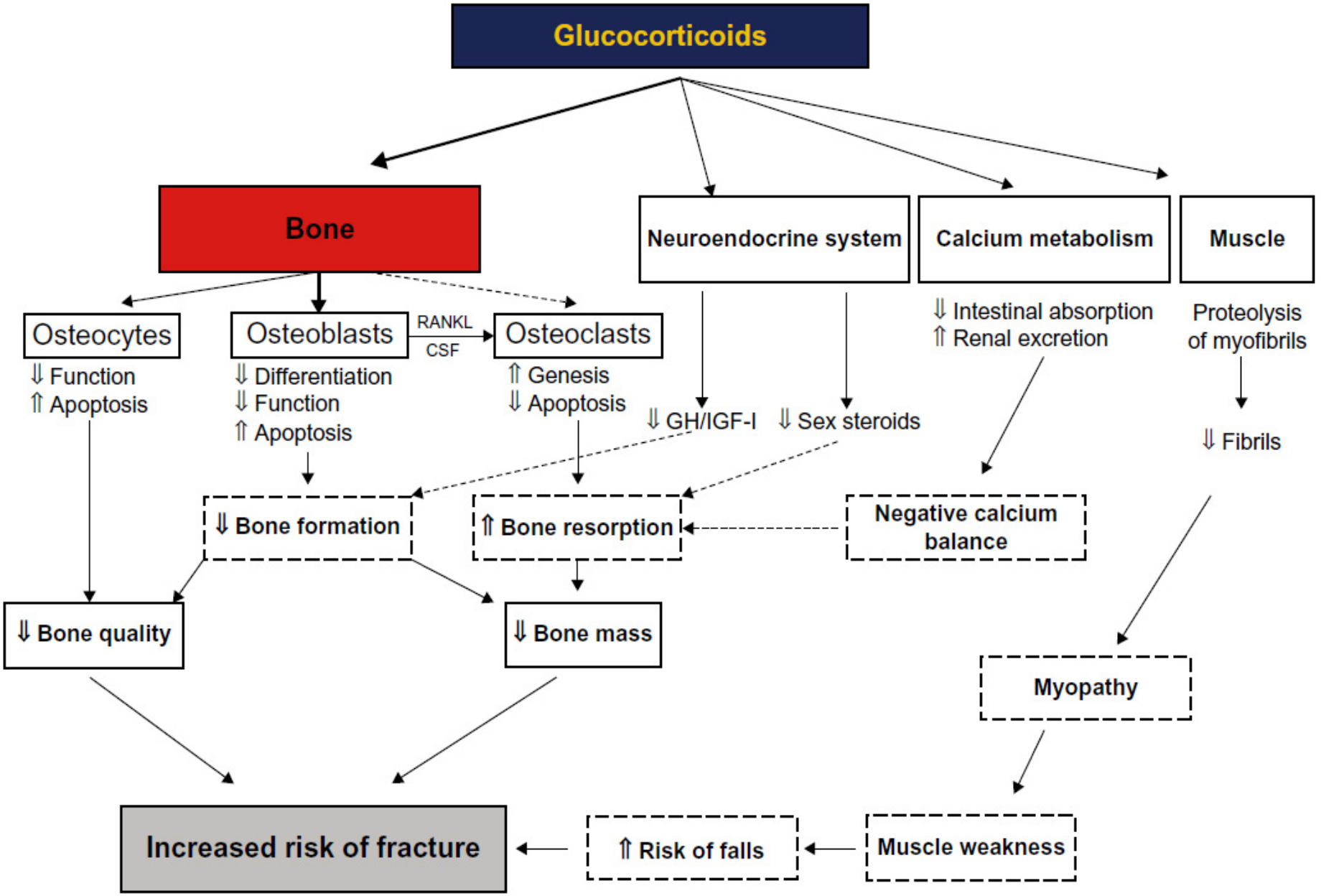
- The annual incidence of vertebral and non-vertebral fracture from the **control arms of GIO-clinical trials** was
  - 5.1% per year chronic steroid use
  - 2.5% per year in patients new to steroids
- In **RA patients** fracture incidence rate:
  - >15 mg/day prednisone (16.0 per 1000 person-year)
  - < 15 mg/day prednisone (5 to 9 per 1000 person-years).
  - after discontinuation of steroids the fracture incidence returned to baseline levels only after 12 months
- In **older Caucasians** with **polymyalgia and giant cell arteritis**
  - incidence fracture rates approximately 14.5 per 1000 person-years, 65% higher than in control population.

Steroid Osteoporosis - Incidence

- In COPD patients increase risk of osteoporosis – depending on use of oral steroids, smoking, BMI and decreased mobility.

- A Cochrane systematic – 2-3 years of usual doses of inhaled glucocorticoids showed no evidence of increased risk of fracture or loss of BMD.

- Inhaled steroids > 8 years and > 600 μg/day of beclomethasone or equivalent resulted in an increased risk of fragility fractures


Glucocorticoids
Bone
Neuroendocrine system
Calcium metabolism
Muscle
Osteocytes
⇓ Function
⇑ Apoptosis
Osteoblasts
⇓ Differentiation
⇓ Function
⇑ Apoptosis
RANKL
CSF
Osteoclasts
⇑ Genesis
⇓ Apoptosis
⇓ GH/IGF-I
⇓ Sex steroids
⇓ Intestinal absorption
⇑ Renal excretion
Proteolysis of myofibrils
⇓ Fibrils
⇓ Bone formation
⇑ Bone resorption
Negative calcium balance
⇓ Bone quality
⇓ Bone mass
Myopathy
Increased risk of fracture
⇑ Risk of falls
Muscle weakness

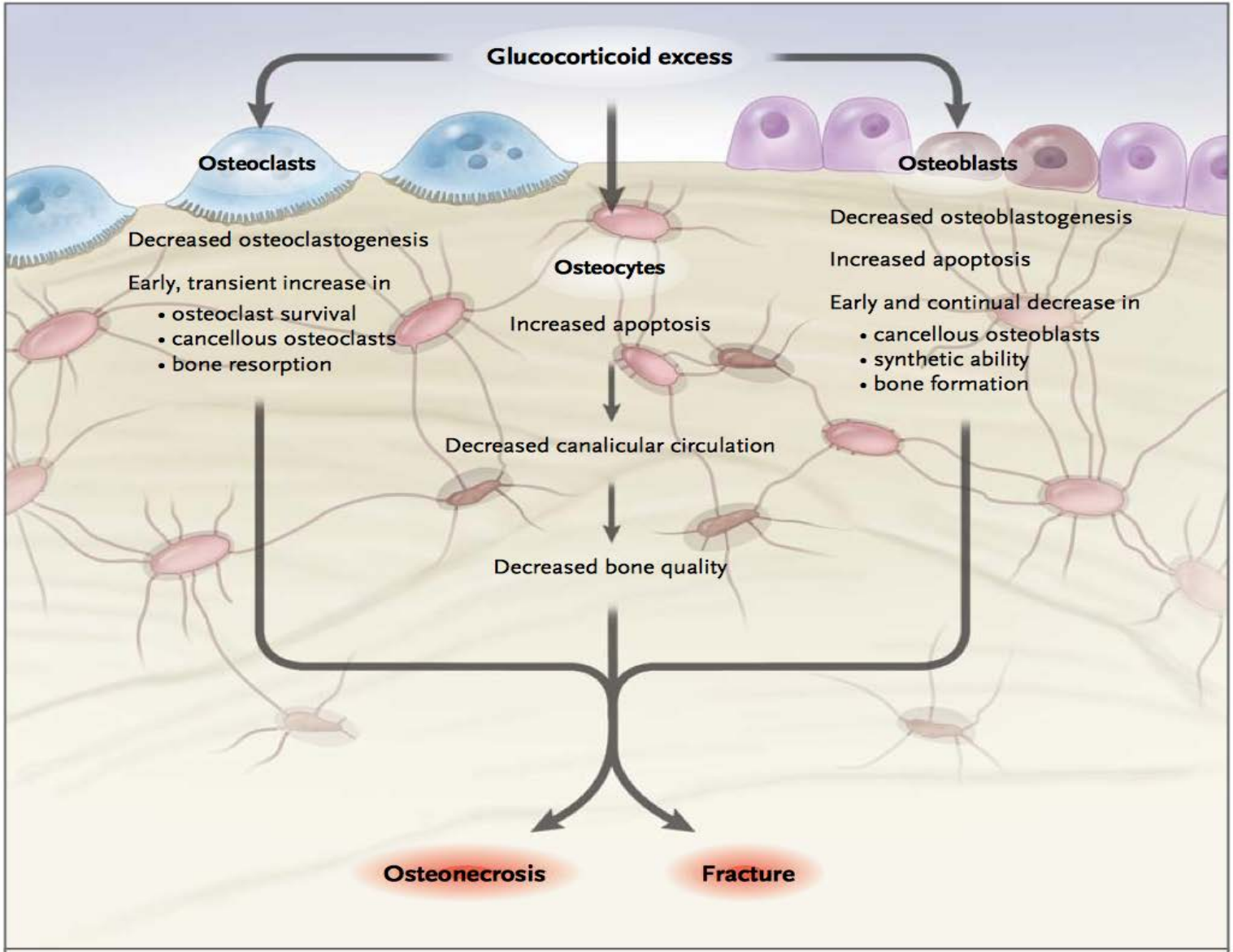


Figure 1. Direct Effects of Glucocorticoids on Bone Cells.

Shown are the adverse skeletal changes that result from an excess of glucocorticoids and lead to osteoporosis and osteonecrosis. The brown, condensed cells are apoptotic osteoblasts and osteocytes. Apoptotic osteocytes disrupt the osteocyte–lacunar–canalicular network.

Steroid Induced Osteoporosis - Clinical

- Dexa BMD may underestimate risk of fractures.
  Fracture risk increases even before bone density changes

- Frax helps to risk stratify but does not take into account dose and duration. FRAX can be adjusted for daily dosage but not for the cumulative dosage or length of use.

- High risk individuals are elderly men and women, postmenopausal women, and individuals with other risk factors including underlying disease.

- Other risk factors are age, low BMI, smoking, alcohol and IV pulsed steroids.

Prevention and Treatment

- Use as little steroid as possible and use topical over systemic. Optimize the use of steroid sparing agents and DMARDs

- Calcium 1200 mg vitamin D3 2000 -5000 iu depending on body weight.

- Weekly alendronate or risedronate or IV Zolendronic acid. IM Denosumab, Rare SERMS and Calcitonin.

- Anabolic agents Teriparatide and Abaloparatide and the newer agent Romozosumab in high risk patient with osteoporotic fractures or very low T scores and elderly.

GIOP Guidelines – Initial Fx risk Assessment

- ACR 2017 - Baseline FRAX/ BMD (within 6 months of GC initiation)
- IOF/ECTS 2012 - Clinical risk factor (i.e., FRAX without BMD); if risk intermediate: BMD
- NOGG 2017 UK - UK FRAX model (GC-adjusted: medium dose 2.5 -7.5 mg/d; high dose ≥ 7.5 mg/d)
- SIM/Italian - 2016 - DeFRA (FRAX derived Fx risk assessment GC-adjusted)

GIOP Guidelines - Treatment

- ACR - **First line:** (in order of preference: oral BPS, IV BPS, teriparatide, denosumab), (raloxifene for PM women none of the medications listed above is appropriate). **Second line:** If Fx, ≥ 18 months of Rx or ≥ 10%/year loss of BMD: teriparatide or denosumab or consider IV BPS if poor absorption/poor adherence.
- IOF/ECTS - First line - all meds no Raloxifene
- NOGG UK - First line*:* oral BPS, Second line: IV BPS or teriparatide
- Italian - **Without OP Fx:** First line: alendronate, risedronate, zoledronic acid. Second line: denosumab
- **With OP Fx:** First line: teriparatide. Second line: denosumab, zoledronic acid. Third line: alendronate, risedronate, ibandronate, strontium ranelate

Study		Saag[5]	Cohen[6]	Reid[7]	Saag[8]	Reid[9]		Saag[26]	
Study drug		Alendronate	Risedronate	Risedronate	Teriparatide	Zoledronic acid		Denosumab	
Comparator		Placebo	Placebo	Placebo	Alendronate	Risedronate		Risedronate	
Design		Treatment	Prevention	Treatment	Treatment	Prevention	Treatment	Prevention	Treatment
Study sites		22	28	23	67	54		79	
Study length (years)		1 (+1 extension)	1	1	1.5 (+1.5 extension)	1		1 (+1 extension)	
Study size (patients enrolled)		561	228	290	428	288	546	290	505
Mean age (years) (56–69 years)		55	62	58	56	56	53	66	61
Postmenopausal women (%) (51–63%)		49	46	53	78	69	64	59	63
Premenopausal women (%) (1–2%)		22	20	9	2.5	0.4	4	5	10
Men (%) (35–47%)		29	34	38	20	32	32	36	27
Ethnicity (% white)		88	N/S	N/S	72	N/S		84	90
Prednisone equivalent inclusion criteria		⩾7.5 mg/day	⩾7.5 mg/day	⩾7.5 mg/day	⩾5 mg/day	⩾7.5 mg/day		⩾7.5 mg/day	
Mean prednisone equivalent dose (mg)	Baseline	18	21	15	7.5 (median)	10 (median)	10 (median)	16	12
	End of study	9	11	13	N/S	N/S	N/S	N/S	N/S

T-score inclusion criteria		N/A	N/A	N/A	T-score ⩽2.0 or ⩽1.0 with fracture	N/A	N/A	N/A	T-score ⩽2.0 or ⩽1.0 with fracture
Mean lumbar spine T-score at baseline		1.0 (g/cm^2)	–0.7	–1.7	–2.5	–1.0	–1.4	–1.0	–2.0
Baseline osteoporosis defined by bone mineral density (%)		32	N/S	23	N/S	N/S	N/S	N/S	N/S
Prevalent vertebral fractures (%)	Study drug	15	30	33	30	N/S	N/S	14	26
	Comparator/placebo	17	29	37	25	N/S	N/S	18	32
Calcium supplementation mg/day		800–1000	500	1000	1000	1000		1000	
Vitamin D supplementation IU/day		250–500	None	400	800	400–1200		800	
Underlying conditions (%)	Rheumatoid arthritis (23%)	30	40	40	48	38	13	33	43
	PMR/GCA (22%/6%)	23	34	18	4	20	5	35	7
	SLE (N/S)	19	15	8	12	9	16	2	6
	Asthma or COPD (19%)	10	4	20	13	4	8	2	11
	Sarcoidosis (N/S)	3	N/S	N/S	N/S	N/S	N/S	0	2
	IBD (5%)	5	N/S	N/S	2	N/S	N/S	N/S	N/S
	Neurologic diseases	7	1	3	N/S	N/S	N/S	1	5

Outcomes of GIOP clinical trials.

Study		Saag[5]	Cohen[6]	Reid[7]	Saag[8]	Reid[9]		Saag[10]	
Study drug		Alendronate	Risedronate	Risedronate	Teriparatide	Zoledronic acid		Denosumab	
Comparator		Placebo	Placebo	Placebo	Alendronate	Risedronate		Risedronate	
Design		Treatment	Prevention	Treatment	Treatment	Prevention	Treatment	Prevention	Treatment
Lumbar spine change (%)	From baseline	+2.9	+0.6	+2.9	+7.2	+4.1	+2.6	+3.8	+4.4
	From comparator/placebo	+3.3	+3.4	+2.5	+3.8	+1.4	+2.0	+3.0	+2.1
Total hip change (%)	From baseline	+2.7	+1.4	+2.4	N/A	+2.0	+2.8	+1.7	+2.1
	From comparator/placebo	+3.4	+4.4	+1.4	N/A	+1.4	+2.3	+1.5	+1.5
Femoral neck change (%)	From baseline	+1.0	+0.8	+1.8	N/A	+1.4	+1.3	+0.9	+1.6
	From comparator/placebo	+2.2	+3.8	+2.1	N/A	+1.0	+1.3	+1.1	+1.0
New vertebral fractures (%)	Study drug	2.3	5.7	5	0.6	1.3		3.0	
	Comparator/placebo	3.7	17.3	15	6.1	0.8		4.4	
New non-vertebral fractures (%)	Study drug	4.4	3.9	8	5.6	N/S		4	
	Comparator/placebo	4.4	5.9	6	3.7	N/S		3	
Vertebral fracture risk reduction (%)		38 (ns)	67 (ns)	67 (ns)	90 ($p <$ 0.01)	N/A		31 (ns)	
Number needed to treat to avoid a vertebral fracture		71	9	10	18	N/A		71	

GIOP - Clinical trials – Alendronate

- In a 12-month randomized, placebo-controlled clinical trial, 477 patients in GIOP - daily ALN 5 and 10 mg
  - Increased BMD 2.1 and 2.9% increase in L-spine BMD vs 0.4% decline in placebo.
  - FN BMD 1%, 1,2% and -1.2%. Bone loss in placebo pts
  - Bone loss was duration dependent - 0.8% in 4mo, - 1.4% in 4-12 mo and 2.9% after 12 mo.
- In 208 patients in the open-label extension study at 2 yrs.
  - **Vert fractures 0.7% on ALN vs 6.8% in placebo.**

- Observational data from a Swedish national database - ALN significantly reduced the risk of hip fracture in 1802 GIOP on ALN 1802 matched GIOP controls (**HR 0.35, 95% CI, 0.22–0.54)**

GIOP - Clinical trials – Zolendronic Acid

- Of 833 GIOP IV Zoledronic acid 5 mg (416 pts) V/S 5 mg oral Risedronate(417 pts)

- Higher BMD increase in IV Zol 4.06% compared to 2.71% in the lumbar spine in treatment arm 2.6% vs 0.6% in the prevention arm at 12 mo.

- **No difference in fracture rate** - possibly due to a **low fracture rate** in the population under analysis in **an active comparator** study that did not require a BMD inclusion criteria.

GIOP - Clinical trials – Teriparatide

- 18 month clinical trials 428 pts 214 each Teriparatide ALN 10 mg daily TP was superior to ALN.
- Small number of vertebral fracture at 24 and 36 months (0.6% vs 6.1% and 1.7% vs 7.7% respectively).
- No difference in non-vertebral fractures 5.6% vs 3.7%.
- Lumbar spine BMD increased 7.2% vs 3.4%

- Consider teriparatide in selected, high-risk patients (i.e., older adults starting higher dose steroids, multiple prior fractures, and very low initial bone mass), potentially even as an initial GIOP drug.

Teriparatide vs Alendronate in GIOP: 36 mo.

- BMD - 11.0% versus 5.3% for lumbar spine, 5.2% versus 2.7% for total hip, and 6.3% versus 3.4% for femoral neck ($P < 0.001$ for all)
- Teriparatide increases from baseline in (PINP) and (OCN) ($P < 0.01$), and increases (CTX)
- ALN decreases in PINP, OC, and CTX
- **Vertebral #** TP vs ALN (3 [1.7%] of 173 versus 13 [7.7%] of 169; $P = 0.007$
- **Non-Vert #** (16 [7.5%] of 214 TP vs 15 [7.0%] of 214 ALN ; $P = 0.843$)

GIOP – Meta analysis – Vertebral Fx

- A 2016 meta-analysis on bisphosphonates for GIOP included 27 randomized controlled trials containing 3075 patients.

- In this analysis, 7.7% of people experienced a new vertebral fracture in the control arm compared with 4.4% in the bisphosphonate arm

- Overall fracture risk reduction was 43% with bisphosphonates (95% CI, 9.0 to 65.0%).

- Aromatase inhibitors Induced bone loss

Aromatase inhibitors

- Letrozole, Anastrozole, Exemestane.

- Enhances menopausal bone loss and increases risk of fractures. 18-20% fracture incidence over 5 yrs. 2-3% increase for each additional year of AI.

- Breast cancer patients had fracture incidence rate ratios of 1.25 (95% CI: 1.23–1.28) and 1.18 (95% CI: 1.14–1.22). These ratios remained significantly increased for 10 yrs.

- Women taking aromatase inhibitors were at an increased risk of fracture as compared with women taking tamoxifen (HR 1.48; 95% CI: 0.98–2.22).

International Expert GP

- All women on AI therapy with ≥1 of the following
- T-score ≤ –2.0.
- Any 2 of the following risk factors
  - T-score < –1.5
  - age >65 yr,
  - low BMI (<20 kg/m ^{2}),
  - family history of hip fracture,
  - personal history of fragility fracture after age 50,
  - oral corticosteroid use >6 mo
  - smoking

Prevention and Treatment

- Zolendronic acid – IV 4 mg every 6 months 5 yrs
  - 1065 pts L spine BMD LS 4.39% TH 1.9%
  - 632 pts L spine BMD LS 6.19% TH 2.57 %
  - 395 BMD /558 BMD LS 4.94% TH 1.22%
  - 527 pts BMD LS 5.98% TH NA

- Risedronate – 35 mg weekly
  - 150 BMD/260 pts BMD 1.1% and -0.7%
  - 908/1410 pts BMD 1.1% and Hip -0.7%

- Meta Analysis:
  - Early Breast Cancer Clinical Trials Gp (EBCTCG), decreasing the incidence of bone recurrence by 34% and breast cancer specific mortality by 17% .

Prevention and Treatment

- Denosumab – 60 mg every 6 months
  - 252/252 pts BMD L Spine 6.2% and TH 2.7%
  - 3420/3420 pts BMD L spine 10.2% and TH 7.92%
  - Fracture risk OR 0.53 (CI 0.333–0.85, p=0.009)

- ONJ risk 1% per year.

- **Androgen Deprivation Therapy**

Gnrh – Agonists Androgen Deprivation

- Luprolide, goserelin, triptorelin, historelin
- Used in treatment of Endometriosis, premenopausal breast cancer, prostate cancer
- Decreases in BMD by 2 - 5% in the first year and the risk of hip and vertebral fractures increases to 20 - 50% at 5 years
- IV BPS, Denosumab, oral BPS
- Alternatives to ADT include antiandrogens, such as bicalutamide, flutamide, and nilutamide, in men without bone metastases.

- **Progesterone only contraception**

Pathophysiology - Progestins

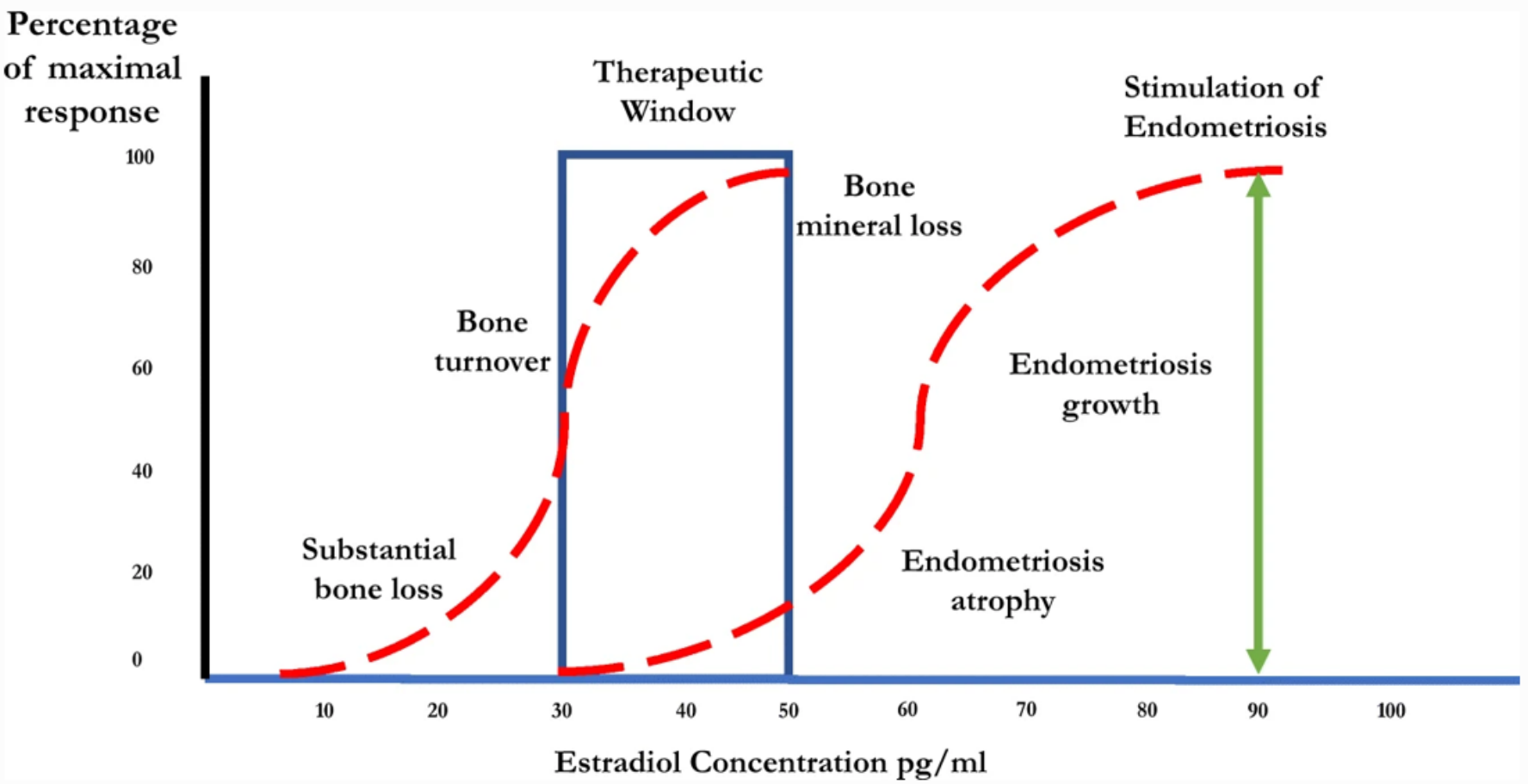
- Progestins - androgenic, antiandrogenic, glucocorticoids. Mineralocorticoid effect. Variable effect on E2 levels.

- DMPA - suppresses ovarian production of estrogen and deterioration of bone mass. MPA inhibits gonadotropin secretion of LH and FSH. Decrease peak bone mass.

- MPA exhibits corticosteroid properties and can decrease osteoblast differentiation by occupying the glucocorticoid receptor. Stopping after 2 years may reverse bone effects.

- Androgenic progestins, including nortestosterone and norethindrone, may have a positive effect on bone mass.

Bone Health - Estradiol levels



The estrogen threshold theory. Modified from Barbieri [11]

Effect of Progestins - bone

From: Bone health in estrogen-free contraception

Dienogest 37 pg/ml (Momoeda et al. [44])
Levonorgestrel 120 pg/ml (Rice et al. [45])
Etonogestrel 90 pg/ml (Beerthuizen et al. [46])
DMPA 26.6 pg/ml (Miller et al. [47]) and 25.6 pg/ml and 35.1 pg/ml (Walsh et al. [28])
Drospirenone 48.7 pg/ml (Duijkers et al. [50])
Desogestrel 54.4 pg/ml (Rice et al. [51])

Oral Progestins – Bone Density

- 9 breastfeeding women using POPs vs 19 women using barrier methods However, half of the control group (*n* = 10) was formula feeding. Although all women showed decline in BMD which was less in POP users.
- Implant - not associated with bone loss. Estradiol well maintained.
- Threshold theory postulated by Barbeiri
- Group A: The use of progestin-only contraceptives leading to an estradiol level between 30 and 50 pg/ml or higher does not seem to lead to an accelerate bone loss.
- Group B: Serum estradiol levels between 20 and 30 pg/ml as reported with the use of DMPA seem detrimental to bone health and should therefore be avoided.

- **Antiepileptic Drugs and Osteoporosis**

Anti Epileptic Drugs - Osteoporosis

- There is increased risk of fracture and decreased BMD and bone loss with AEDs

- Increased fractures may be due to falls related to the underlying disease(stroke, cerebral palsy), seizures and AED use.

- Other risk factors include age, sex, smoking, duration of AED treatments and type of AEDs (enzyme inducers and non enzyme inducers) and single or combination.

AED and fracture risk: meta-analysis

- Increase in fracture risk among users of AEDs involving 1,292,910 participants, with a mean/median age of 36 – 82 years (relative risk (RR) = 1.86; 95% confidence interval (CI) 1.62–2.12).

- Both liver enzyme-inducing antiepileptic drugs (LEI AEDs) and non-LEI AEDs were associated with an increase in fracture risk, although the estimate for LEI AEDs was higher than that of non-LEI AEDs (RR = 1.18; 95% CI 1.11–1.25).

- Use of phenobarbiturate (PB), topiramate (TPM) and phenytoin (PHT) suggested an increase in fracture risk of 78%, 39% and 70%, respectively

- Chunhong Shen, et al Bone. 2014 Jul;64:246-53.

Antiepileptic Treatment - with Bone Loss:

- AEDs, decrease BMD - 10 and 16 percent below controls.
- Men and women appear to be affected similarly
- A meta-analysis of 12 studies – AED use associated with significant deficit of BMD in both hip and spine with mean Z-score deviations of -0.56 and -0.38, respectively.
- However, a cross-sectional study of premenopausal women found BMD to be normal despite AED monotherapy for an average of 8 to 13 years
- In children, reduced BMD at axial and appendicular sites has been described but not as consistently as in older adults.
- Age, AED duration, monotherapy or polytherapy, type of drug (enzyme-inducer phenytoin, phenobarbital, carbamazepine) or non–enzyme inducer (valproate, ethosuximide, lamotrigine, clonazepam).

Pathophysiology - AEDs

- Xenobiotics upregulate 25(OH)D3-24-hydroxylase (CYP24) in the kidney through activation of PXR. This enzyme catalyzes the conversion of 25(OH)D to its inactive metabolite (24,25-dihydroxyvitamin) rather than to its active metabolite (1,25-dihydroxyvitamin D).

- AEDs are associated with decreased fractional calcium absorption, secondary hyperparathyroidism, and increased bone turnover.

- Phenytoin and carbamazepine inhibit osteoblasts. Only phenytoin has been shown to inhibit osteocalcin secretion-a hormone that regulates calcium in the bone.

- Topiramate and Zonisamide - chronic metabolic acidosis.
- Valproic acid – Fanconi's syndrome - Osteomalacia
- Newer agents Levetiracetam appears to be safe

- **Miscellaneous Drugs Osteoporosis and Fractures**

Proton Pump Inhibitors

- Several large observational studies suggest that PPI use is associated with a modest increase in osteoporotic fracture risk hip 20-60% and spine 40-60%. Greater than 1 year increases the odds ratio (OR) to around 1.44, and more than 7 years of exposure, the OR increases to 4.55

- Mechanism not known - calcium malabsorption due to low acid suggested. Risk decreases when PPIs are DCed

- PPI use and BMD have found no clear association

- Dose and duration dependent and other risk factors especially smoking and BPS use.

Thiazolidenediones – Fractures

- Once used extensively for treatment of type 2 DM. Now limited use in select patients with Type 2 DM
- A meta-analysis of 10 randomized trials and two large observational studies indicate TZDs double fractures in women with type 2 DM but not in men.
- Usually non vertebral extremities small bone fractures, upper arm and pelvis. Risk is related to duration of use of TZDs
- A meta-analysis of three population-based European cohort studies also found a 1.2-1.5 fold increase in fractures in women but not men on TZDs. But a UK study showed higher risk in men and women and even young women.

Thiazolidinediones – Mechanism of OP

- Peroxisome proliferator-activated receptor γ (PPARγ) expressed in stromal cells of the bone marrow, osteoblasts, and osteoclasts, and plays an important role in the differentiation of stromal precursor cells into OB.

- TZDs impair the differentiation of osteoblast precursors, thereby preventing bone formation.

- TZDs may act on bone remodeling by increasing adiposity of bone marrow, decreasing aromatase activity, and promoting OC differentiation, leading to increased bone resorption.

SGLT-2 inhibitors - Fractures and bone loss

- In diabetic patients with moderate renal impairment, 9.4% of patients treated with dapagliflozin (10 mg/d) experienced bone fractures. No fractures were observed in placebo-treated patients.

- Canagliflozin (300 mg/d) accelerated loss of total hip BMD compared to placebo (−2.1% vs. −0.9%) during a 104 week trial in diabetic patients 55- 80 years of age.

- In the Canagliflozin Cardiovascular Assessment Study, canagliflozin was associated with an increased incidence of fractures: 4.0% of canagliflozin-treated vs. 2.6% of placebo-treated patients.

SGLT-2 inhibitors – Mechanism of bone loss

- SGLT2 inhibitors promote weight loss, and the magnitude of weight loss was correlated with a biomarker for bone resorption (collagen type 1 β-carboxy-telopeptide). Weight loss explained only a small percentage (~3%) of the variance of bone resorption biomarkers.

- SGLT2 inhibitors can induce postural hypotension, which may increase the risk of falls and fractures.

- Finally, women receiving canagliflozin (300 mg) experienced a 9.2% decrease in estradiol levels

- Increase in Serum P 0.61 mg/dl due to decreased GFR and increased proximal tubular phosphate reabsorption. This triggered increase in FGF 23 by 20% and decrease in 125D by 10% higher PTH 25% lower Uca.

SSRI – increased risk of fractures

- Several studies - SSRIs are associated with bone loss and increased fracture risk. Fracture risk was highest at the hip and nonvertebral sites vs spine. Older men and women. Dose and duration related. Other risk factors smoking.

- Meta analysis: OR for fracture among SSRI - users to be 1.69 (95% CI 1.51–1.90; $r2 = 89.9\%$) OR of 1.73(95% CI 1.51–1.9; $p < 0.001$).

- No decline in BMD. Serotonin receptors found on osteoblasts and osteoclasts regulate bone homeostasis via endocrine, autocrine, paracrine, and neuronal serotonin pathways.

Anticoagulants - Heparin

- Unfractionated heparin (UFH) is associated with drug-induced osteoporosis with long-term, high-dose therapy.

- Bone loss occurs after six months of heparin therapy with daily doses greater than 15,000 units.[3]

- Newer low-molecular-weight heparins (LMWHs), Enoxaparin use resulted in no significant changes in BMD in women treated throughout pregnancy and six weeks after giving birth.[3]

Pathophysiology - Anticoagulants

- Heparin causes increased bone resorption by stimulating osteoclasts and suppressing osteoblast function, leading to decreased bone mass.

- Other proposed mechanisms include depletion of mast cells in bone marrow and enhancement of parathyroid hormone (PTH)

- It is controversial whether warfarin and loss of vitamin K causes impaired bone formation.[3]