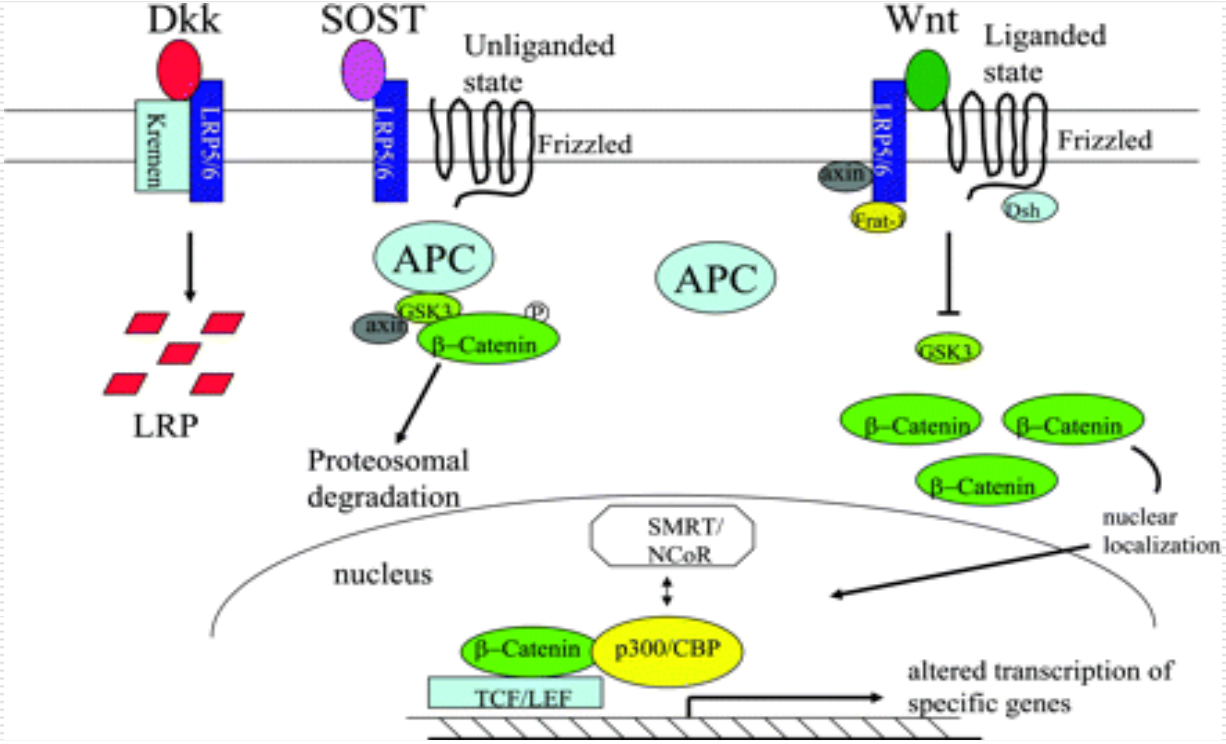
Bone metabolism update

I.Shraga-Slutzky, 2008

Patophysiology of osteoporosis

- *Wnt* signaling in controlling osteoblast differentiation, the accrual bone mass, and bone loss



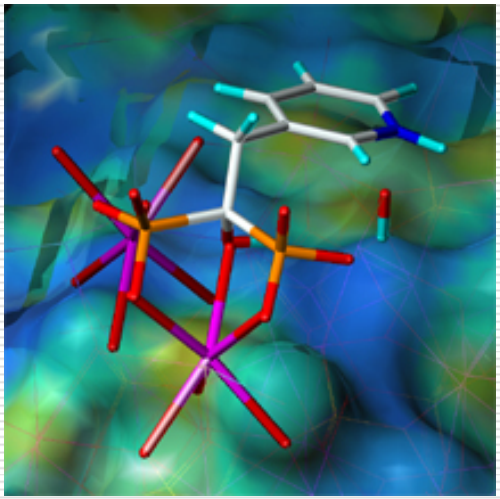
J Clin Invest,2006

Sclerostin

- Sclerostin inhibits the activity of osteoblasts and prevents them from promoting excessive bone formation, **a negative regulator of bone formation**
- ***In vitro*** – inhibits osteoblast differentiation
- ***Animal studies***- transgenic mice – osteopenic , with reduced bone formation
- ***The human high bone mass*** phenotype - enhanced bone formation in the presence of normal bone resorption, d/t mutations of the *LRP5* gene that make it resistant to the inhibitory action of Dkk1,or SOST mutations thereby increasing Wnt signalling
- ***Preclinical study-*** three sclerostin-neutralizing monoclonal antibodies were tested in ovariectomized rats and young monkeys : 5.5-fold increase in the rate of bone formation in lumbar vertebrae, 53 % increase in peak load for the lumbar spine (bone strength)

Mechanisms of action of bisphosphonates: similarities and differences

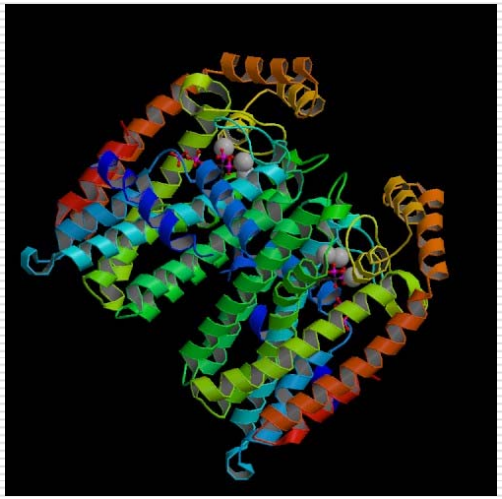
Bone Mineral Affinity



Bone Uptake and Release

Availability, Distribution, Offset of Action

FPPS Enzyme Inhibition

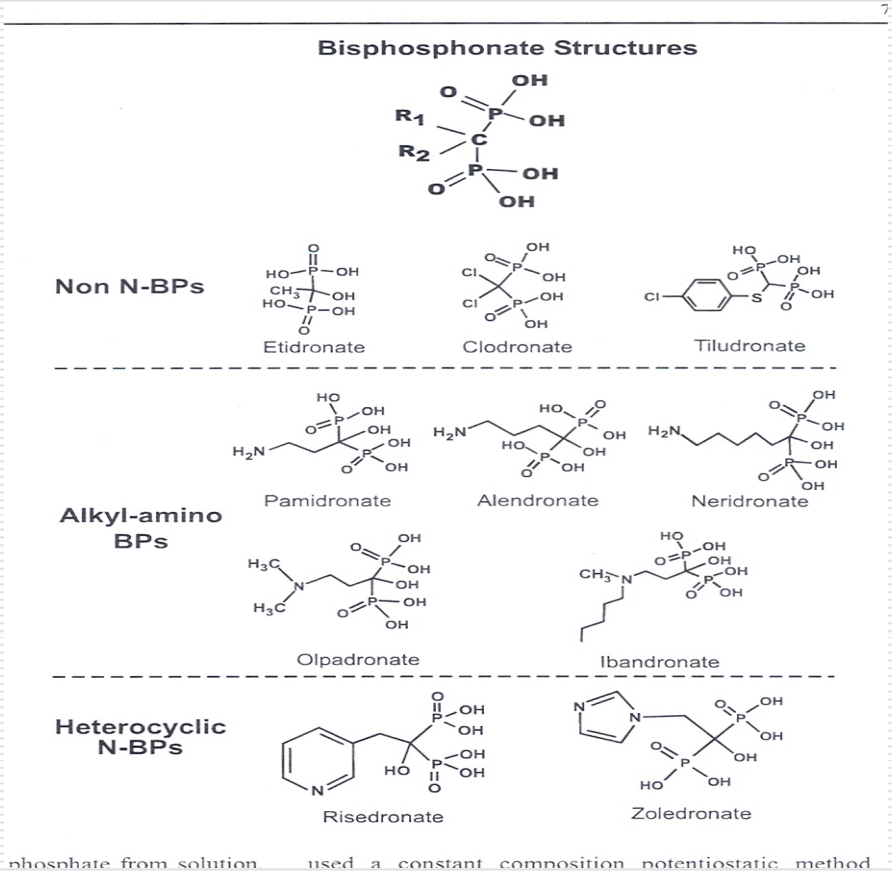


Osteoclast Function

Potency

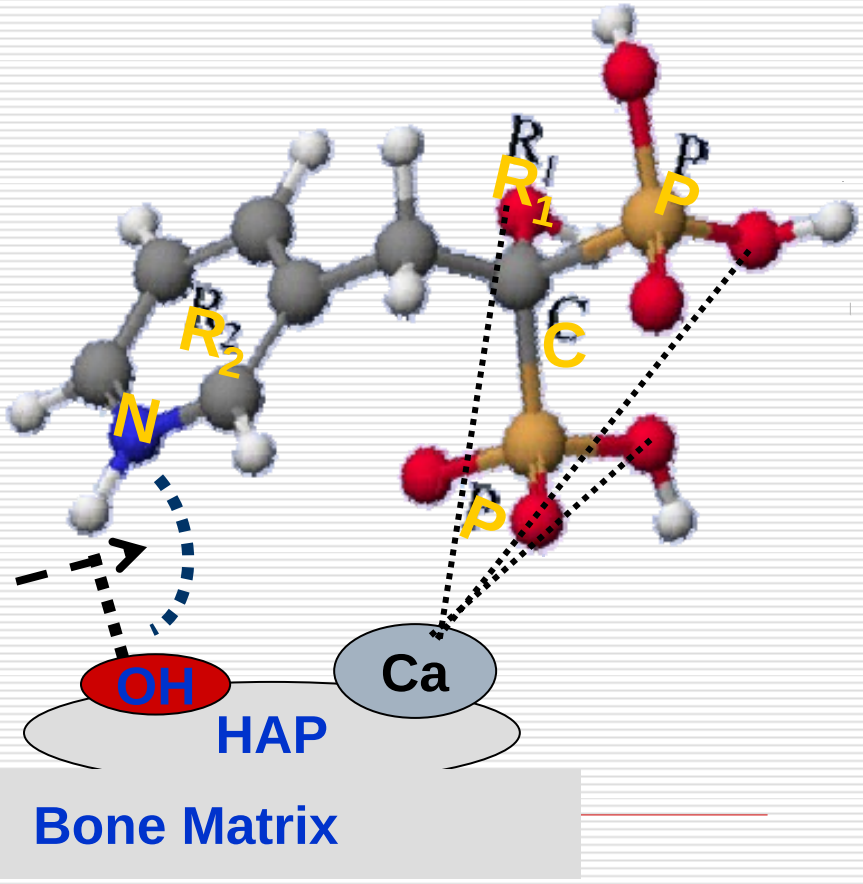
Ebetino FH, et al. J Bone Miner Res, 2005
Russell RG, Osteoporos Int, 2008

Bisphosphonates structures



Bisphosphonate Attachment to Hydroxyapatite at the Bone Surface

- All BPs have high binding affinity via Ca^{2+} interactions
- H-bonding by the R^2 N-group (N to H-O bond on HAP surface); requires close proximity, which is influenced by N-H-O bonding angle



Differentiator for mineral binding affinity

I.S

Ebetino FH, et al. J Bone Miner Res 2005;20(Suppl 1):S259

Physiochemical differences

- **The adsorption of BP**

  at pH 7.4 : ris<zol< iba< eti<alen

  Ebetino FH, Rev Contemp Pharmacother, 1998

- **Influence of molecular charge (zeta potential)**

  different electrical charges on their N in the R group at pH 7.4: ris<zol<iba<alen

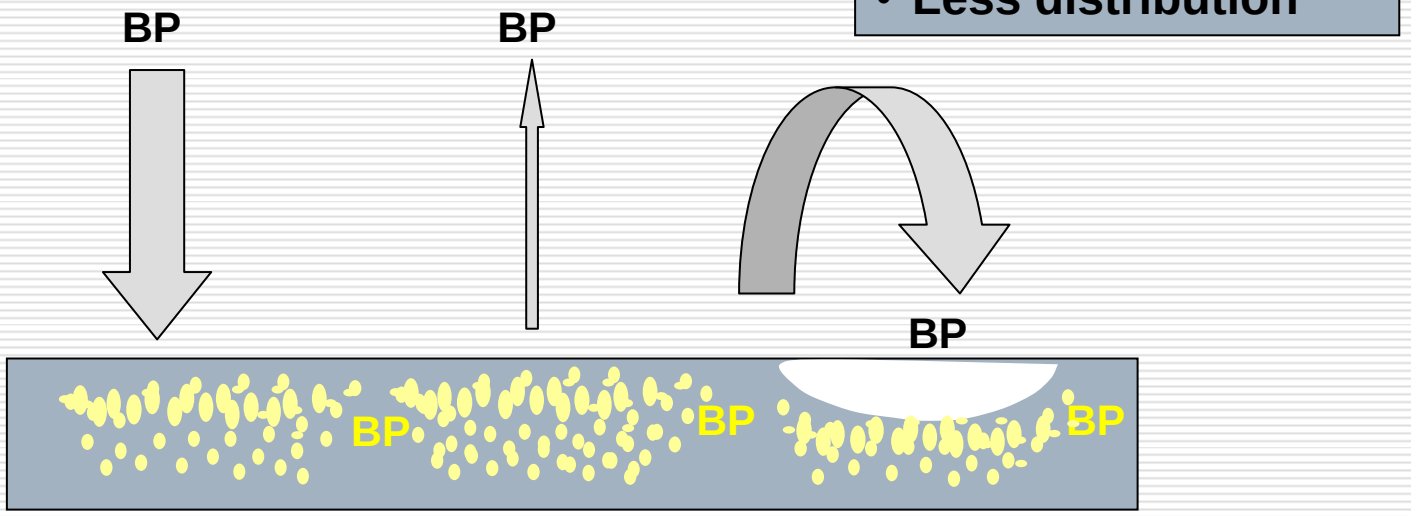
  Nancollas GH, bone, 2006

- **Effects on crystal size, crystal growth, aggregation, interactions with collagen and other charged matrix molecules …**

Uptake, Detachment and Recirculation of BPs on Bone: Effect of Binding Affinity

Higher affinity BPs e.g., alendronate, zoledronate Vs
Lower Affinity BPs e.g., risedronate

- **Stronger uptake**
- **Lower desorption**
- **Slower offset**
- **Higher reattachment**
- **Less distribution**

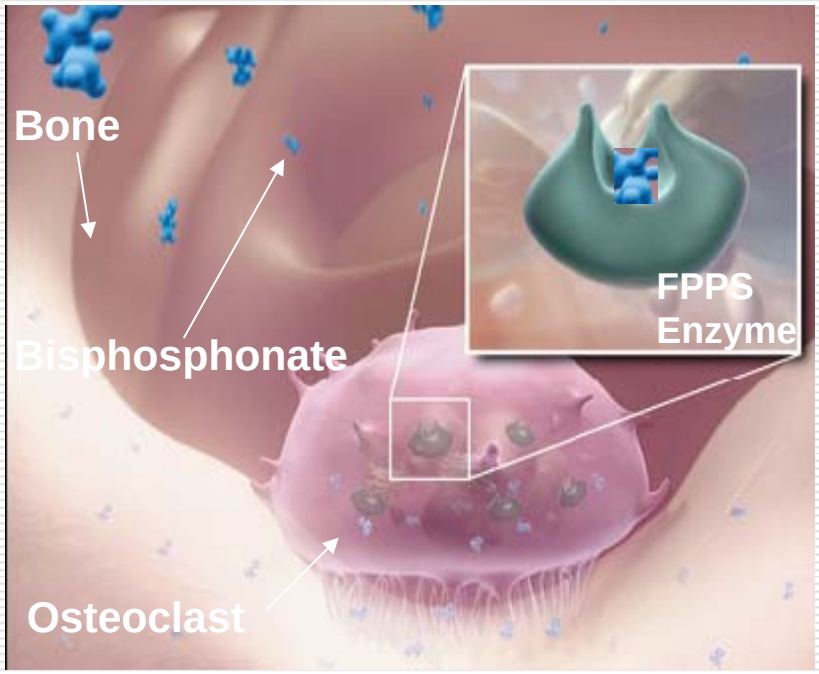


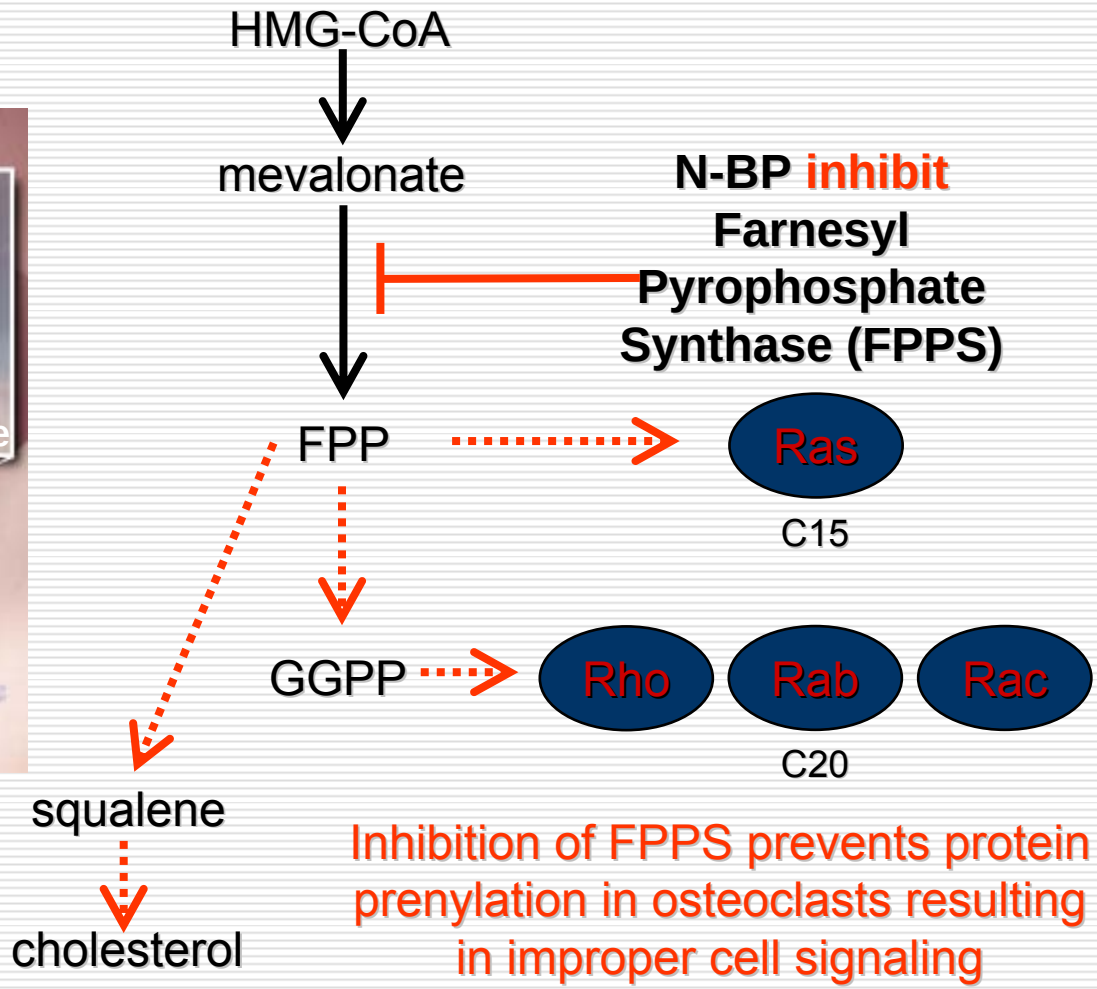
- BPs can be detected in body fluids many months after injection
- Higher Affinity BPs may diffuse less well in bone and remain nearer accessible surfaces

Nancollas GH et al. Bone. 2006; 38:617-627

Nitrogen-containing Bisphosphonates mechanism of osteoclast inhibition

RIS, ZOL, PAM, ALN, IBN





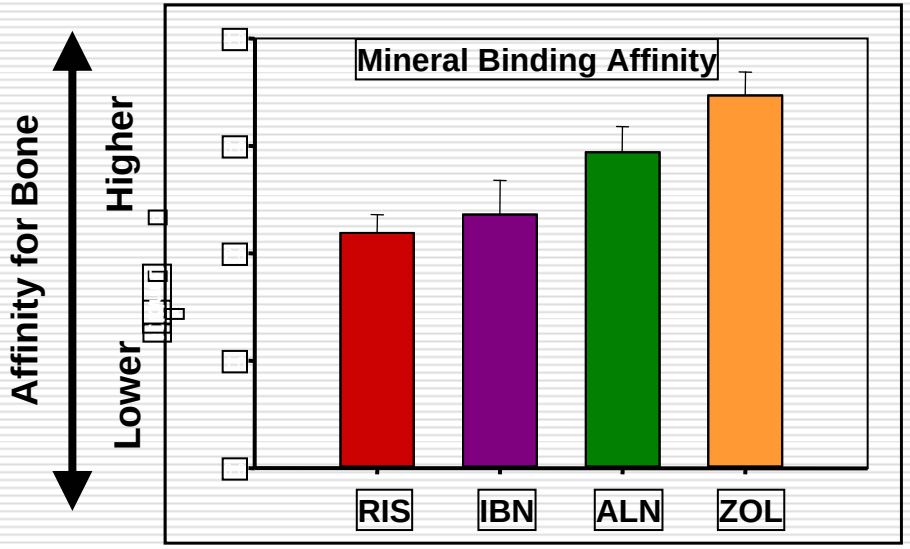
Inhibition of FPPS prevents protein prenylation in osteoclasts resulting in improper cell signaling

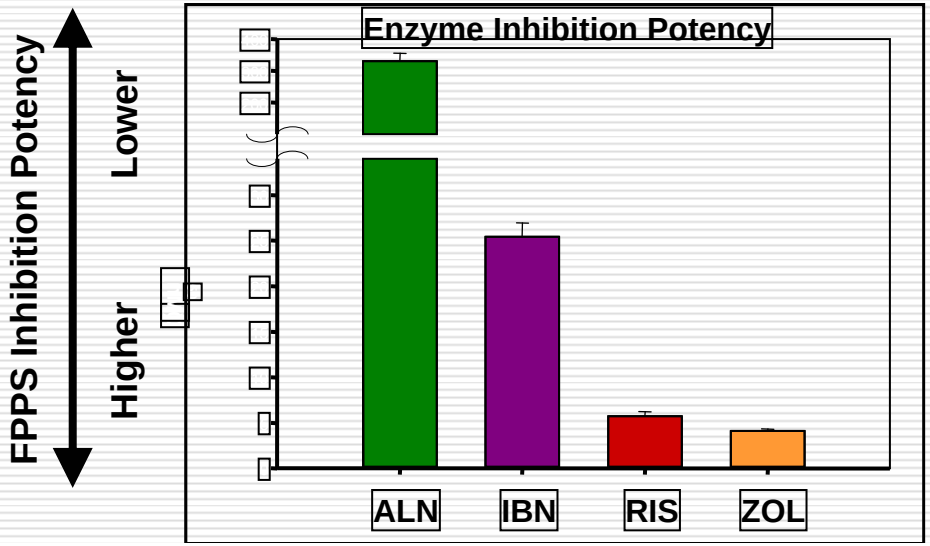
Adapted from Rogers MJ. Curr Pharm Des 2003;9:2643-58.

Rank Orders of Bisphosphonate Activity are Distinct for Mineral Affinity and Enzyme Inhibition

Bone Mineral Affinity

FPPS Enzyme Inhibition





Russell RG, Osteoporos Int, 2008

Potential effects on osteocytes, osteoblasts

- *In vitro*- prevention of osteoblastic cell apoptosis (GC, etoposide) is mediated by connexin 43 hemichannel opening and activation of the extracellular signal-regulated kinases (ERKs): 16 different BP/ 6 lack of pro-apotptic activity in osteoclasts but retain anti-apoptotic activity in osteoblasts, osteocytes

Plotkin LI, Bone, 2006

Clinical differences

Effect on BMD

FACT: 833 postmenopausal , 64.5 yr. osteopenic women received 70 mg AL vs 35 mg ris : at 24 months greater gain in the spine BMD with AL ~ 2 % *Bonnic S, JCEM, 2006*

Speed of onset of antifracture effect *Russell R, Osteopor Int, 2008*

	Alendronate	**Risedronate**	**Zoledronic acid**
RCT, radiographic fractures	24 months	12 months	12 months
Pooled, post-hoc, clinical vertebral fractures	12	6	36
Pooled,post-hoc, nonvertebral	24	6	24
Observational, for hip fractures	12	6	-

Home message

- **Alendronate-**higher mineral binding associated with greater reduction in bone turnover can compensate for lower cellular activity to achieve pharmacological potency
- **Risedronate**- one of the strongest inhibitors of FFPs, has low binding affinity and a wider distribution within bone (more cortical regions influence and the osteocytes network)
- **Zolendronate-**strong inhibitory activity on FFPs and osteoclasts, coupled with a high affinity for bone mineral **(** that possibly restricts the distribution within the bone)

Osteonecrosis of the Jaws and Biphosphonates

- Since 2003, case series: BON
- Exposed bone in the maxillofacial area that has persisted >8 weeks, history of current or previous BP, no history of radiation

AAOMS Task Force on BON, 2007

ASBMR, 2007

- **DD**-periodontal disease, caries-related pathology
- **Epidemiology** – systematic review, 1966-2006: 368 cases /18 cases in non-cancer patients (13-ALN, 1-RIS, 1-ALN+ZOL,3-i.v. BP for Paget's *Ann Intern Med, 2006*

  ASBMR Task Force- 63 cases in PMO or Paget's

Data are limited, lack of uniform definition, not all cases are reported or reported more than once

Postmarketing Surveillance-Merck:170 cases of BON with ALN-

0.7 reports/ 100,000 patients-years of exposure

Procter &Gamble:20 cases with RIS

Osteonecrosis of the Jaws and Biphosphonates

RCT- no cases of BON were reported with oral BP(>17,000 patients with ALN, >44,000 patients-years with RIS)

None of these trials included specific reporting of dental AE or adjudication of suspicious dental finding

HORIZON- 1/1

Population-based prevalence studies, 2006-postal survey of oral surgeons in Australia - 0.01-0.04% with ALN(0.09-0.34 % after dental surgery)

German registry of BON- 3/780,000 patients on BP-<1/100,000

- 1/3 of all cases- no history of intra-oral trauma
- 5%-ALN+RIS
- **Etiology-**1. The accumulation of microcracks d/t reduction of bone turnover

  2. Higher concentration of BP may be taken in the jaws because of heightened daily bone remodeling requirement, or when osteoclast activity increases in response to trauma or infection

  3. Potential antiangiogenic effect of BP (preclinical studies)

Osteonecrosis of the Jaws and Biphosphonates

- ASBMR Task Force on BON, 2007:- patient information
  - Good dental hygiene and care
  - patients with history of BP>3 years: nonsurgical perodontal therapy' documented informed consent before implant surgery, cessation of BP before and after invasive procedure

Home message

- The rate of BON in patients with OP or Paget's disease is <1/100,000
- The rate of BON in cancer patients on frequent, high doses of BP is ~ 0.1%
- The risk –benefit ratio favors their continued use in patients with cancer, Paget's , and osteoporosis

Atypical skeletal fragility with long-term biphosphonate therapy

- **Odvina CV et al , JCEM, 2005, Visecruna M, JCEM, 2008**

12 p. (10 postmenopausal women, 1 premenopausal women, 1 men) with atypical fractures and delayed healing after long-term, combined antiresorptive therapy

TABLE 1. Clinical data

Patient	Age (yr)/ sex	Diagnosis	Duration of alendronate treatment (yr)	Other medications	Incident fractures (yr on alendronate)	Delayed/absent healing on alendronate (fracture site)	Fracture healing yes/no (months off alendronate)
Group A							
1	55/F	PO	6	Ca, D	Sacrum (6)	NA	No (12)
2	76/F	PO	7	Ca, D	Vertebra, rib (7)	NA	Yes (6)
3	52/F	POpen	8	Ca, D	Femoral shaft (8)	4 months (femoral shaft)	No (9)
4	68/M	IO	8	Ca, D	Bilateral femoral shaft (8)	NA	No (8)
Group B							
5	68/F	PO	3	E2, Ca, D	Sacrum, ischium (3)	3 months (ischium)	Yes (8)
6	70/F	PO	5	E2, Ca, D	Pubic rami (3)	2 yr (pubic rami)	Yes (4)
7	67/F	POpen	5	E2, Ca, D	Bilateral femoral shaft (5)	9 months (left femoral shaft)	Yes (5)
Group C							
8	49/F	GIO (asthma)	3	Prednisone, Ca, D	Proximal femur (1)	2 yr (femur)	No (8)
9	64/F	GIO (fibromyalgia)	4	Prednisone, Ca, D	Metatarsal, proximal femur (3)	8 months (proximal femur)	Yes (3)

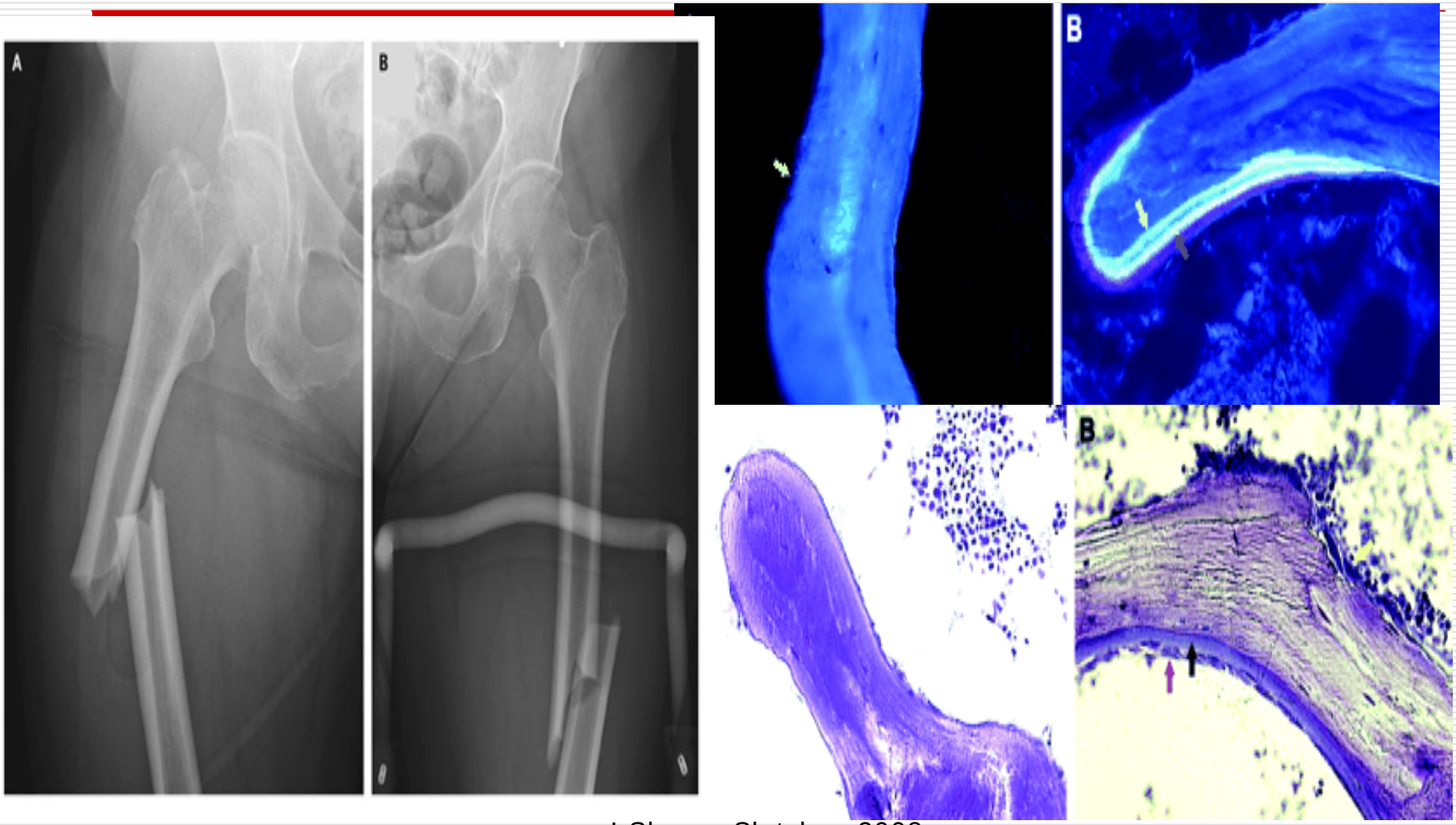
PO, Postmenopausal osteoporosis; POpen, postmenopausal osteopenia; IO, idiopathic osteoporosis; E2, estrogen; Ca, calcium; D, vitamin D; NA, not available or not applicable; F, female; M, male.

Turnover

	Patient									Control (mean ± SD)
	1	2	3	4	5	6	7	8	9	
BV/TV (%)	14.3	15.2	14.7	9.7	9.4	12.2	17.2	10.9	8.9	21.2 ± 4.9
OV/BV (%)	0.42	0.66	0.17	0.07	0	0	2.5	0.89	0.05	1.85 ± 1.07
O.Th (μm)	4.3	8.0	4.6	4.5	0	0	10.2	4.0	3.9	9.3 ± 2.1
Ob.S/BS (%)	1.7	0	0.14	0	0	0	0.7	3.6	0.2	4.4 ± 2.0
ES/BS (%)	3.5	9.3	9.2	5.6	0.9	2.1	4.3	1.3	1.7	4.0 ± 2.0
Oc.S/BS (%)	1.0	0.3	0.35	0.12	0	0.2	0.35	0.3	0.1	0.7 ± 0.7
dLS/BS (%)	0	0	0	0	0	0	0	0	0	4.3 ± 2.9
sLS/BS (%)	0.6	0	0.42	0.44	0	0	0.5	0	0.3	6.0 ± 4.1
BFR ($\mu m^3/\mu m^2/yr$)	1.0	0	0.7	0.2	0	0	0.6	0	0.4	15 ± 0.8

BV, Bone volume; TV, total volume; OV, osteoid volume; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S/BS, osteoclastic surface/bone surface; dLS, double-label tetracycline label; sLS, single tetracycline label. BFR, Bone formation rate calculated as ½ × sLS/BS × MAR (micrometers per day) obtained from cortical doubled-labeled surfaces as previously described (19). BFR for four patients was calculated as ½ × sLS/BS × 0.3 μm/d as previously described (19).

- **Lenart, NEJM, 2008-** subtrochanteric fractures
  15 postmenopausal women, ALN- mean 5.4±2.7 yr
  63%- bilateral 1/3 steroid use



I.Shraga-Slutzky, 2008

- Fracture healing was absent or incomplete in 9 patients, complete after 12 months of teriparatide in 1 p.

- 51 cases of subtrochanteric insufficiency fractures on alendronate treatment were described in the orthopedic literature , 2007-2008

- **Clinical characteristics:**- atypical sites(sacrum, pubis, femoral shift- frequently bilateral)
  - concomitant treatment by E2, GC
  - prodromal thigh pain
  - delayed healing
  - relatively normal Tsc FN

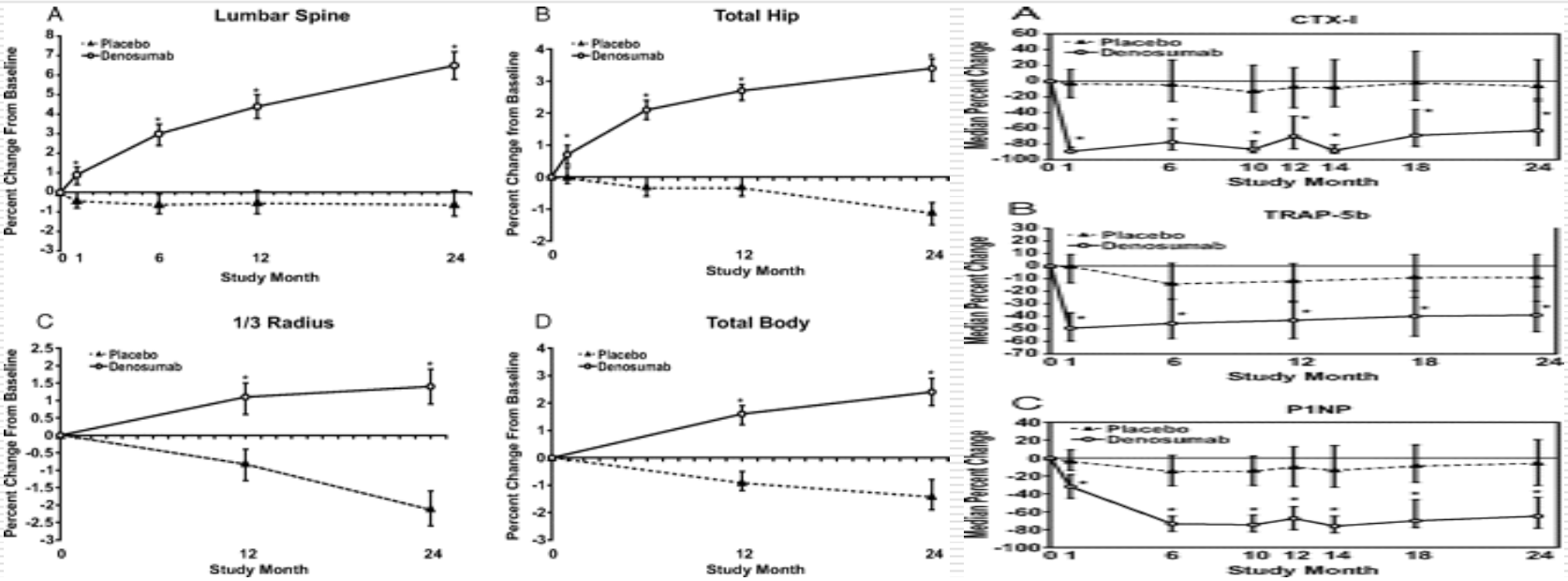
- These cases are likely to be attributed to underlying skeletal abnormality rather than to the prescribed treatment

  (asymptomatic heterozygotes for chloride channel defects or osteoclast proton pump deficiencies – type II AD osteopetrosis

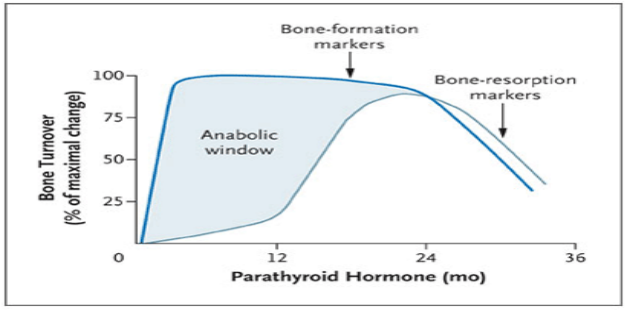
Novel therapies

- **Strontium ranelate,** both anabolic and antiresorptive properties.
  RR for vertebral fractures by 40% in postmenopausal women with osteoporosis
  RR for all nonvertebral fractures by 16%
  RR for all major fragility fractures(hip, wrist, ribs, humerus) by 19%
  TROPOS, N Engl J Med, 2004

- **Denosumab ,** human MAb directeg against RANK-L
  Phase 3, osteopenic women +aromatase inhibitor.
  Denosumab n=125 vs placebo n=125 *J Clin Oncol, 2008*



Anabolic window



- PTH initially stimulates bone modeling and only later –bone remodeling
- Greater variability in densitometric responsiveness > BP
- Reduction in cortical bone density is compensated by microarchtectural changes (periosteal apposition, increase in cortical thickness , and an overall increase in cross-sectional area)
- **Postmenopausal osteoporosis**

1-34 *Neer at al,2001-* severe PMO,20mcg,40 mcg, placebo, 21 months :
spine BMD**+10**%, total hip BMD**+3**%, 1/3 rad **0**%
Decrease VF **50**% NVF **35**%

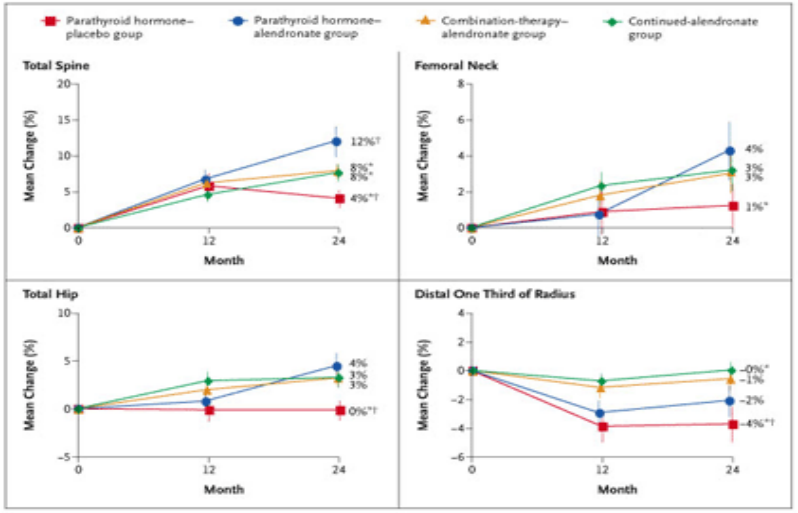
Extension up to 30 months,2005 - 60%- BP, sustained fracture reduction.
↓hip BMD if no BP
↑hip BMD if +BP

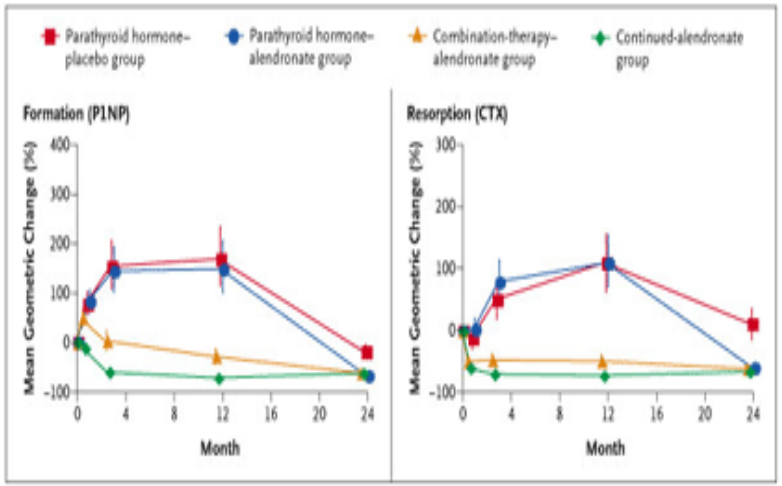
1-84 *Greenspan S,2007* – PMO, 19%- prior VF, different doses and placebo, 18 months: spine BMD+7% total hip BMD +2%
Decrease VF 50-70% , no reduction in NVF

PTH and an antiresorptive agent

- *JBMR, 2004*- 95 postmenopausal women with Tsc<-2.0, R or ALN for
  28 months before 18 months 1-34 PTH:
  R- spine BMD +10%, ALN- spine BMD+4.1%
  bone markers in ALN increased later and reached to 1/3

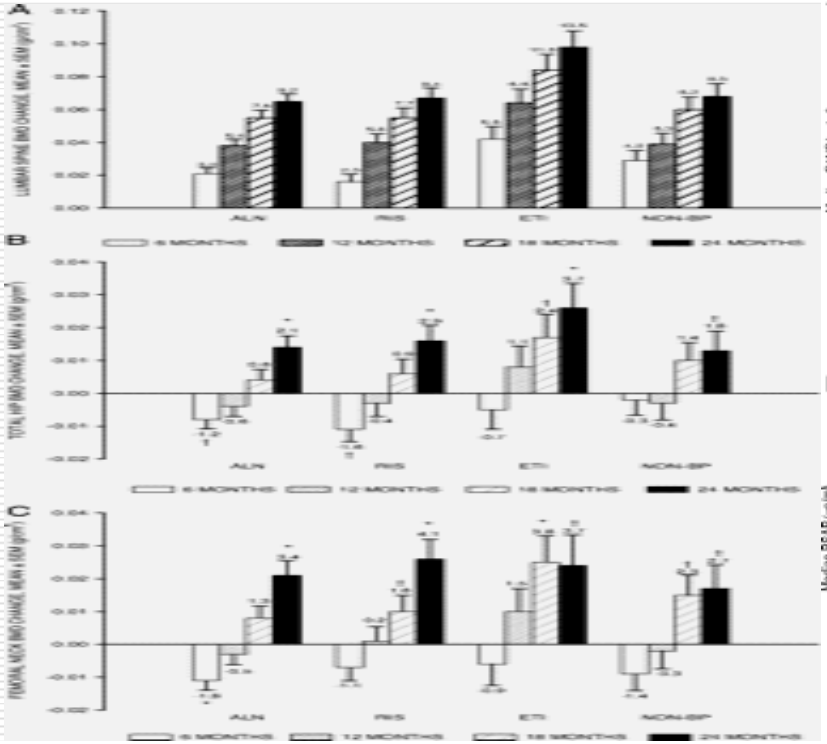
- *Black D, 2005*- n=233, 70 yr, 2 years:
  PTH/ALN , PTH/placebo, PTH+ALN/PTH, ALN/ALN

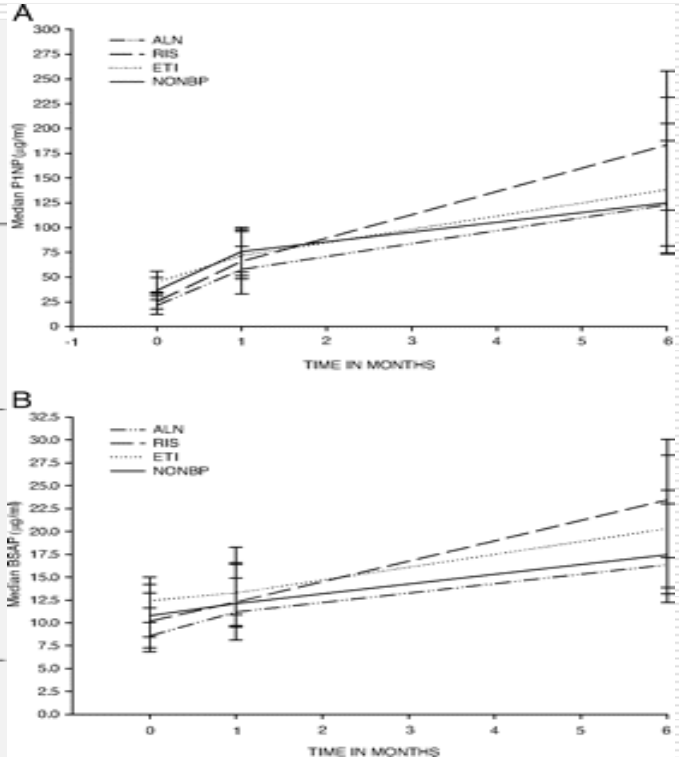




Duration of antiresorptive therapy and lag time didn't affect the BMD response on PTH

- EUROFOS -2-yr prospective, open-label, randomized trial – 865 postmenopausal women with established OP(previous fragility fracture), 95 centers in 10 European countries , 2 yr teriparatide treatment
- 245 p., previous treatment with one antiresorptive drug for a minimum 12 months .





JCEM, 2008

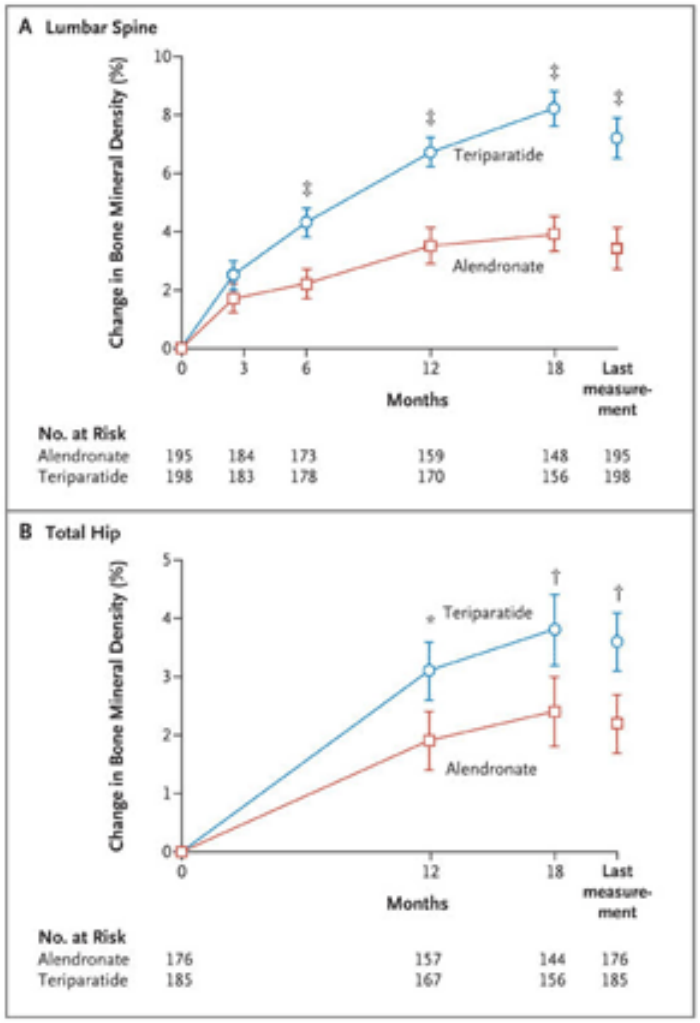
Home message

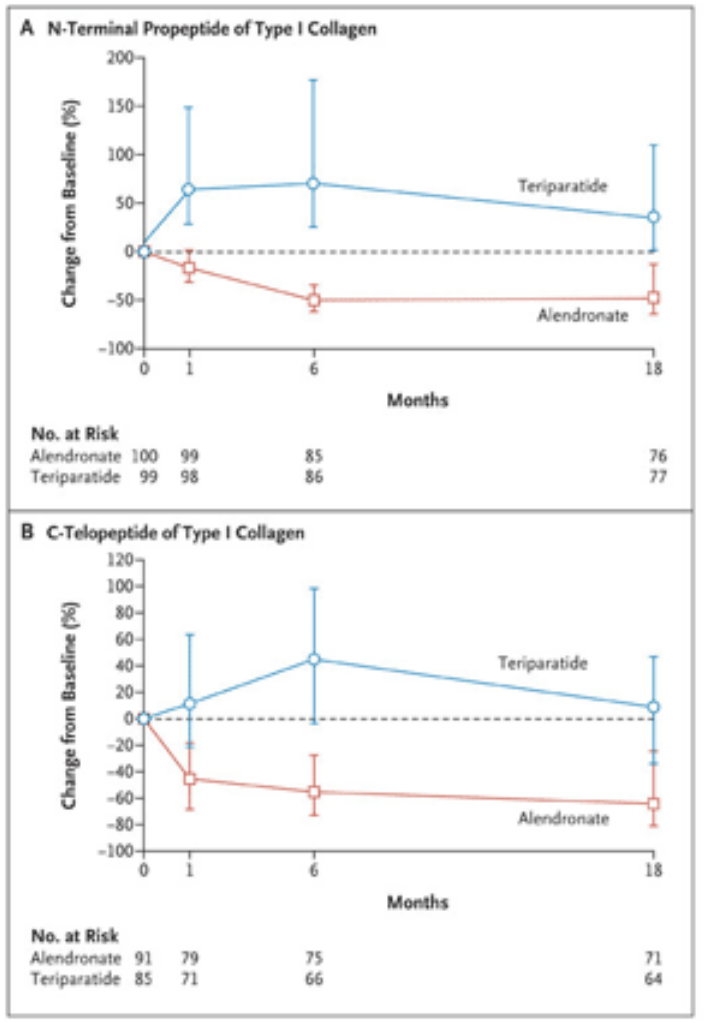
- PTH induces positive effects on BMD and markers of bone formation in postmenopausal women with established OP, regardless of previous long-term exposure to antiresorbtive therapies, duration of antiresorptive therapy and lag time between stopping previous therapy and starting PTH
- The transitory decrease of total hip and FN BMD in all treatment groups at 6 months reverses with longer PTH
- Following PTH therapy with BP is recommended for consolidation

Teriparatide or Alendronate in Glucocorticoid-Induced Osteoporosis

NEJM,2007

- RCT, double-blind, the first 18 months of a 36-month trial : teriparatide vs alendronate in 428 women and men with osteoporosis (22 - 89 yrs) who had received glucocorticoids for at least 3 months (prednisone equivalent, 5 mg daily or more). **214 patients** - 20 µg of teriparatide once daily, and **214** -10 mg of alendronate once daily.
- The mean duration of previous glucocorticoid therapy in the trial was more than 1 year, and the mean baseline lumbar T score was –2.5 — and >2/3 already had a fragility fracture
- 1st outcome -BMD change in at the lumbar spine.
- The 2d outcomes - changes in BMD at the total hip and in markers of bone turnover, the time to changes in bone mineral density, the incidence of fractures, and safety.





The 10 new vertebral fractures in the alendronate group vs 1 fracture in the teriparatide group. The number of new nonvertebral fractures did not differ significantly between groups(8 vs 12)

I.Shraga-Slutzky, 2008

Home message

- For patients with low BMD who are receiving long-term low-dose glucocorticoid therapy **Teriparatide** seems to be associated with **greater** increases in BMD at the spine and hip and with **significantly fewer new vertebral fractures**, with no significant differences between groups in the incidence of nonvertebral fractures or serious adverse events vs **alendronate**
- On the basis of the known pathophysiology of glucocorticoid-induced osteoporosis, teriparatide might be considered as a therapeutic strategy for patients at high risk for fracture.

Serum 25-OH-D concentration and risk for hip fractures

- Nested case-control study within WHI-OS (**prospective cohort, 93 676 women between 1994-1998 at 40 US centers, 50-79 yr**), 400 case-patients with incident hip fracture and 400 control participants , annual questionnaires to report any skeletal events, 08/2004- median follow-up duration-7.1 yr, mean serum 25(OH)D and risk fractures (for every 2.5 nmol/l and 25 nmol/l decrease in 25(OH)D and across quartiles)
- Exclusion-a history of hip fracture, HRT before enrollment, current OP treatment
- 71 yr, 30% > 70 yr, 95% white.

  case-patients: a lower BMI, less physical activity, more likely use GC, poor health status, more smoking ($p<0.01$)

  The average number of falls didn't differ between 2 groups

S. Cummings, Ann Intern Med, 2008

Odds Ratios of Risk for Hip Fracture*

Table 2. Odds Ratios of Risk for Hip Fracture*

25-Hydroxyvitamin D Level	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
Per 2.5-nmol/L decrease‡	1.03 (1.01–1.05)	1.03 (1.01–1.05)
Per 25-nmol/L decrease	1.30 (1.07–1.58)	1.33 (1.06–1.68)
Quartile (according to control group)		
First (9.2–47.5 nmol/L)	1.73 (1.13–2.66)	1.71 (1.05–2.79)
Second (47.6–60.1 nmol/L)	1.08 (0.72–1.63)	1.09 (0.70–1.71)
Third (60.2–70.6 nmol/L)	0.78 (0.50–1.20)	0.82 (0.51–1.31)
Fourth (70.7–121.5 nmol/L)	1.00 (reference)	1.00 (reference)

* We selected and matched case-patients with control participants according to age, race or ethnicity, and blood draw date. Eighteen case–control pairs were missing from our multivariate models because of missing values. We excluded these pairs from our unadjusted models, even when values were not missing, to provide similar risk estimates from the same analytic samples.
† Multivariate adjustment includes age, body mass index, parental history of hip fracture, history of fracture, smoking, alcohol use, total calcium intake, oral corticosteroid use, and geographic region.
‡ *P* value for linear trend = 0.009 for unadjusted and 0.015 for multivariate-adjusted models; models based on a 25-hydroxyvitamin D threshold level of 50 nmol/L fit no better than the linear models.

Cauley, J. A. et. al. Ann Intern Med 2008;149:242-250

Annals of Internal Medicine

Home message

- Community-dwelling women with the lowest 25(OH)D concentration(<47.6 nmol/l) have a significantly greater increased risk for subsequent hip fracture during the next 7 years than did women with the highest concentration(≥ 70.7 nmol/l). The association is linear and doesn't seem to differ by age, BMI, physical activity and falls

- ***5 prospective studies of serum vitamin D and fractures***:

  1.NHANES III, 2008 - RR for hip fractures among patients with 25(OH)D > 60 nmol/l – 0.64 (CI,0.46-0.89)

  2. Swedish women, 2005, those with serum 25(OH)< 52.5 nmol/l , had a 2-fold risk

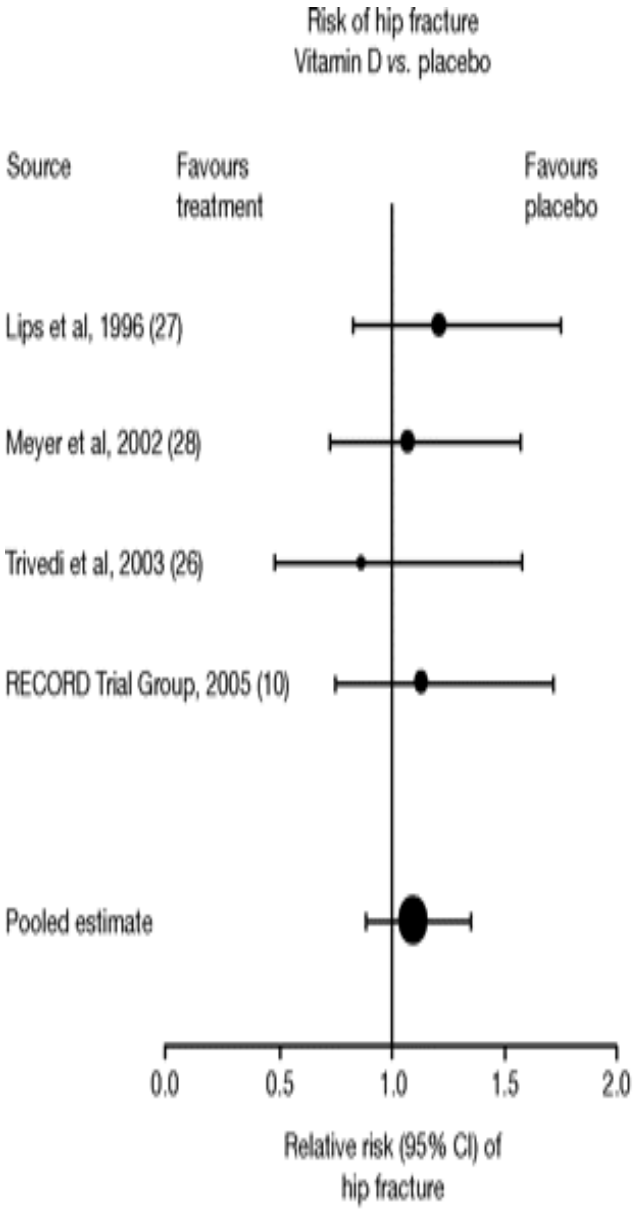
  3. 2 cohort studies,1990, 1998- no significant association

  4. EPIC-study, a nested case-control , 2007- no evidence

  S. Cummings, Ann Intern Med, 2008

Need for Additional Calcium to Reduce the Risk of Hip Fracture with Vitamin D Supplementation: Evidence from a Comparative Metaanalysis of Randomized Controlled Trials, *JCEM, 2007*

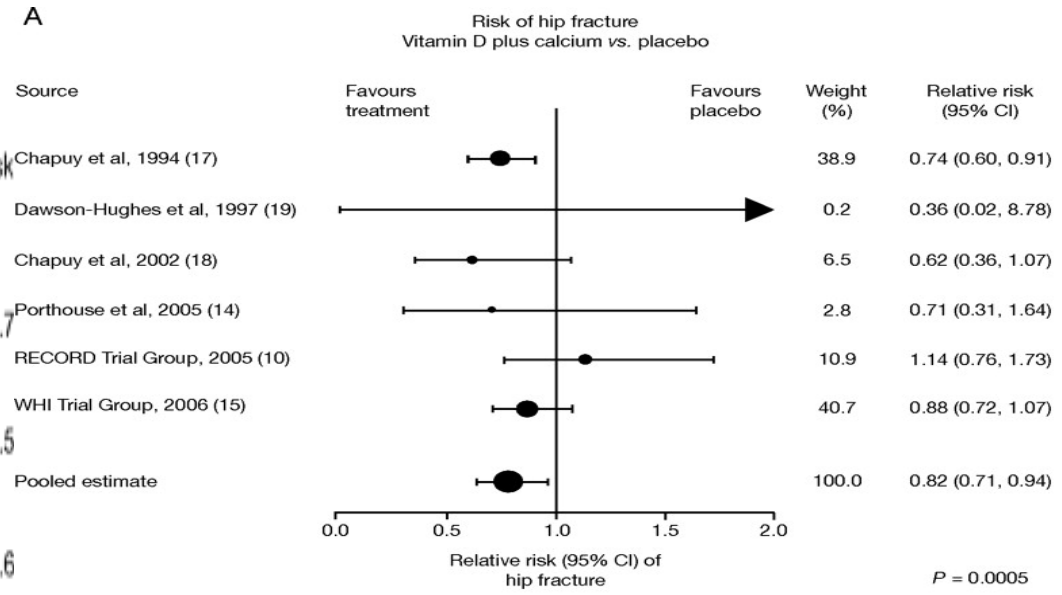
- 4RCTs (9083 patients): RR of hip fracture for vitamin D alone was 1.10 [95% (CI) 0.89, 1.36].
- 6 RCTs (45,509 patients) of vitamin D with calcium supplementation: RR for hip fracture was 0.82 (95% CI 0.71, 0.94). In an adjusted indirect comparison of the summary RRs from the two metaanalyses, the RR for hip fracture for vitamin D with calcium *vs*. vitamin D alone was 0.75 (95% CI 0.58, 0.96). NNT to prevent one hip fracture of 276 (95% CI 165, 843) over 24–84 months. NNT for all nonvertebral fractures was 72



CI = confidence interval

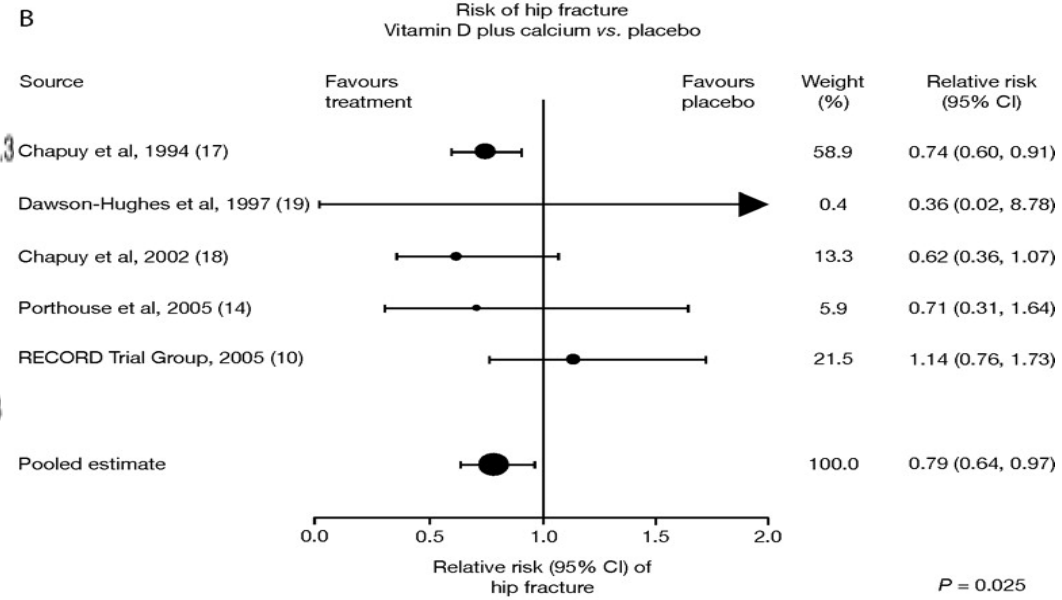
RECORD = Randomised Evaluation of Calcium Or vitamin D

A



CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D
WHI = Women's Health Institute

B

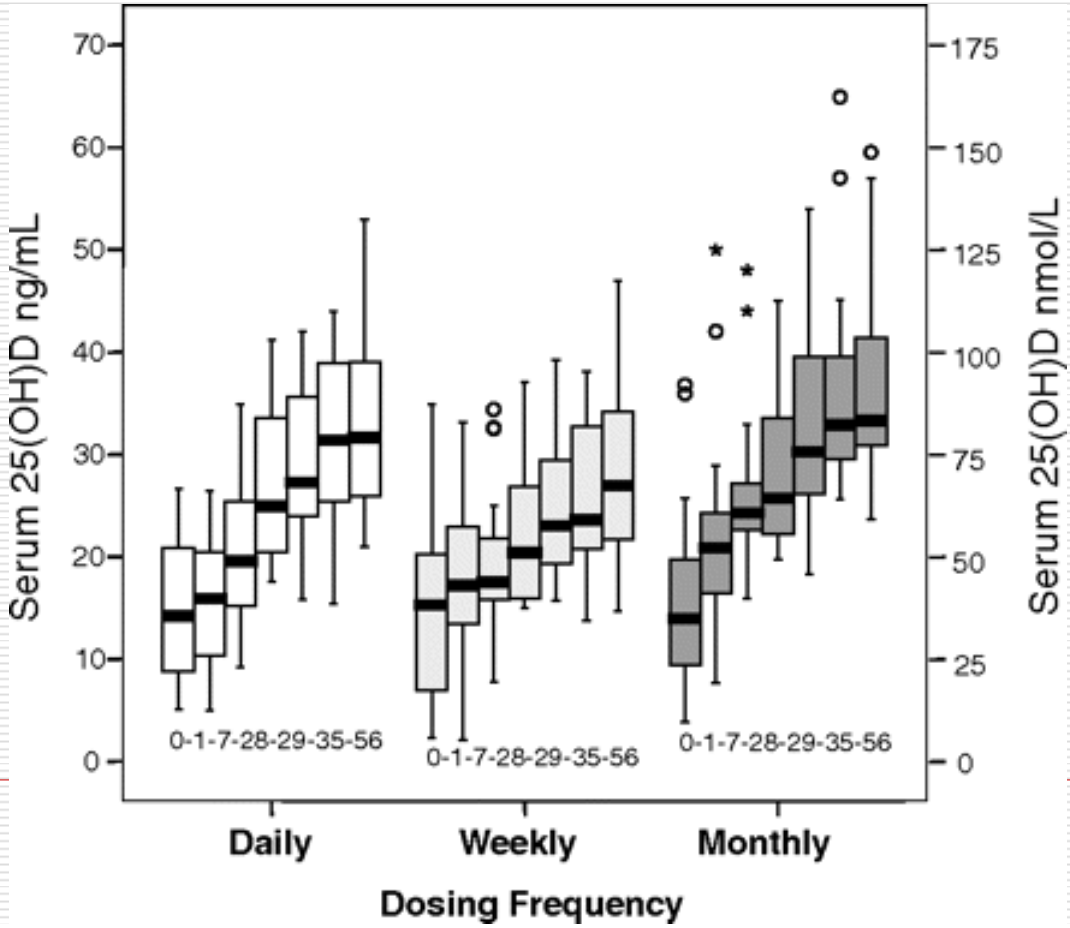


CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D

Monthly Vitamin D3

Ish-Shalom S, JCEM, 2008

- 48 women > 80 yr , after hip fracture repair, 1,500 iU vs 10,500 IU vs 45,000 IU , 2 months



HORIZON

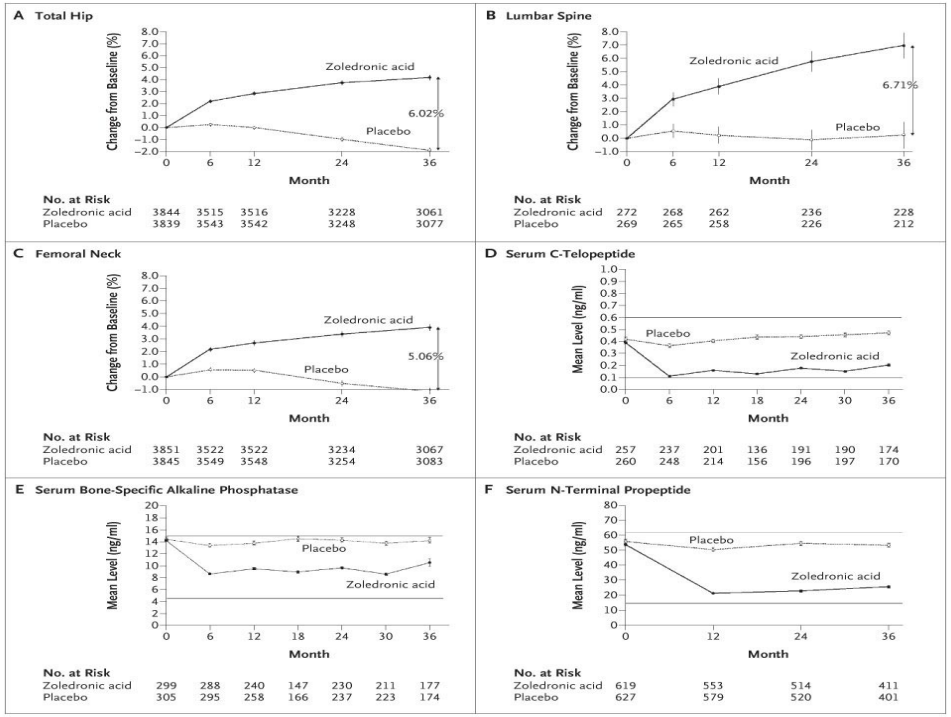
- International, RCT, **1 stratum-** 3889 women, mean 73 yr, i.v. 5 mg zoledronic acid yearly vs. 3876 women, placebo , 3 years, +1000-1200mg Ca, 800-1200 u D
- 1 end-points- new vertebral fracture, new hip fracture
- 2 end-points- BMD, bone turnover markers, safety outcomes

Table 2. Relative Risk of Fracture Incidence in the Two Study Groups.*

Type of Fracture	Placebo	Zoledronic Acid	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. of patients (%)			
Primary end points				
Morphometric vertebral fracture (stratum 1)	310 (10.9)	92 (3.3)	0.30 (0.24–0.38)	<0.001
Hip fracture	88 (2.5)	52 (1.4)	0.59 (0.42–0.83)	0.002
Secondary end points				
Nonvertebral fracture	388 (10.7)	292 (8.0)	0.75 (0.64–0.87)	<0.001
Any clinical fracture	456 (12.8)	308 (8.4)	0.67 (0.58–0.77)	<0.001
Clinical vertebral fracture	84 (2.6)	19 (0.5)	0.23 (0.14–0.37)	<0.001
Multiple (≥2) morphometric vertebral fractures (stratum 1)	66 (2.3)	7 (0.2)	0.11 (0.05–0.23)	<0.001

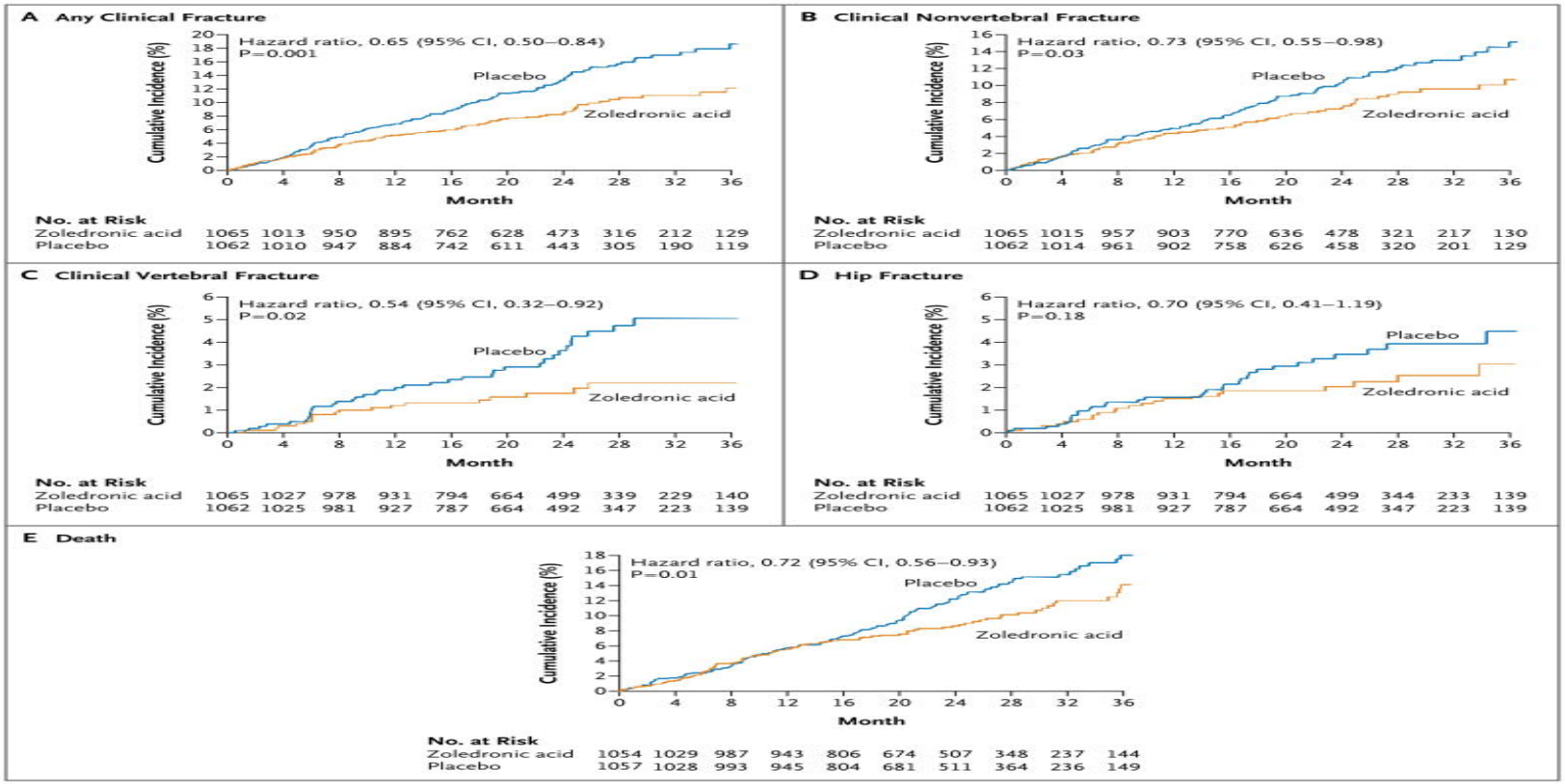
* The percentage of morphometric fractures is the proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture (2853 patients in the placebo group and 2822 patients in the zoledronic-acid group). The percentage of clinical fractures is based on Kaplan–Meier estimates of the 3-year cumulative incidence (3875 patients with clinical fractures in the placebo group and 3861 in the zoledronic-acid group).

† For morphometric vertebral fractures, the relative risk is presented; for all other end points, the adjusted hazard ratio is presented. The significance level for morphometric vertebral fractures is based on an adjusted logistic-regression analysis.



Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture

- From HORIZON- **2 stratum,**1065 p.,i.v. 5 mg zoledronic acid yearly vs. 1062 p., placebo – **within 90 days after surgical repair of a hip fracture,**1.9 yr, + calcium, vitamin D



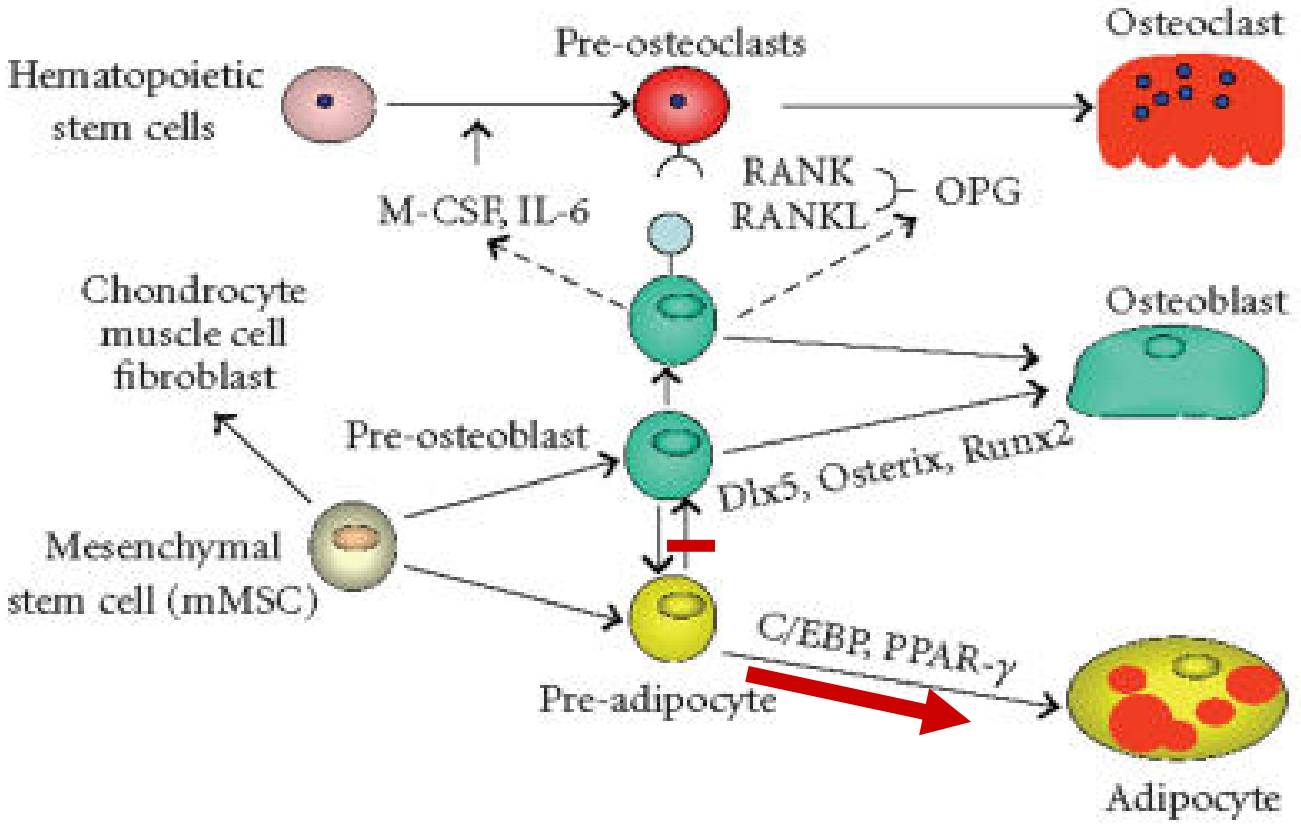
SLC34A3 mutation in patients with Hereditary Hypophosphatemic Rickets with hypercalciuria *Am J Hum Gen, 2006*

- AR disorder that was first described in a large Bedouin kindred (NEJM, M.Tieder, 1985)- hypophospatemia secondary to renal phosphate wasting, rickets , **hypercalciuria** (↑1.25-(OH)D)
- 10 patients - a genome-wide linkage scan combined with homozygosity mapping –SLC34A3 gene on 9q34 (a loss of function of the renal sodium-phosphate cotransporter NaP-IIc)
- 7 patients and their relatives from 5 families –SNP array genotyping
- FGF23 was at normal or low-normal levels

Home message

- HHRH appears to be due to a primary proximal renal tubular cell transporter defect
- **NaP-IIc** plays a key role in phosphate homeostasis
- The AR hypophosphatemic rickets is associated with hypercalciuria
- Unlike for XLH and ADHR, phosphate supplementation alone can cause a complete remission, whereas the addition of vit D can create hypercalcemia, nephrocalcinosis, and renal damage

Diabetes, TZDs and bone loss



Evidence from clinical studies

- **Health ABC**, 2005 : 69/666 used TZD

  Troglitasone(N=22) Pioglitasone (N=30) and/or Rosiglitasone (N=31)

  each year of TZD

  whole body bone loss -1.01%/year

  lumbar spine - 1.23%/year

  trochanter -0.65%/year

  Not using TZD whole body bone loss -0.4%/year

- **ADOPT**, 2006

  4360(42%♀), mean age 57 years , for a median 4 years

  ♀: 9.3% fractures for rosiglitasone RR 2.18(CI:1.52-3.13)

  5.1% for metformin

  3.5 % for glyburide

  ♂ : RR 1.18(CI: 0.77-1.8)

- **Takeda**, Clinical trial database, 03.2007
  24 000 person-years:
  ♀- fracture incidence 1.9/100 person-years
  vs 1.1/100 person-years for placebo or another active drug
  ♂- didn't differ between the pioglitasone and comparison drugs

GlaxoSmithKline(GSK), 02. 2007, Takeda, 03.07:
Letter to Health Care Provider about increased incidence of fractures in women treated with rosiglitasone and pioglitasone

Altered bone and mineral metabolism in patients receiving imatinibe mesylate

NEJM, 2006

- Imatinib is used to treat CML and gastrointestinal stromal tumors.
- Series of 16 patients with hypophosphatemia vs. 8 normophosphatemic patients:
  - ↑ PTH
  - low-to-normal Ca
  - younger
  - higher dose
- ↓ osteocalcin, ↓ DPD, phosphaturia – both groups
- Imatinib could reduce bone remodeling

Increased cortical bone mineralization in imatinib treated patients with chronic myelogenous leukemia , *Haematologia, 2008*

- 17 CML p. treated 2-4 yrs.vs 17 healthy control p.:
BMD of the lumbar spine (+12%) and total hip bone (+12%)

- *in vitro* , animal models: Osteoblasts and osteoclasts are targeted by imatinib that promotes osteoblast differentiation and inhibits osteoclastogenesis, presumably through its action on the colony-stimulating factor 1 receptor (C-FMS) and platelet derived growth factor receptor (PDGFR)

- Imatinib seems to uncouple bone formation from bone resorption in favor of the former, disturbing bone homeostasis and leading to a net increase in bone mineral density

I.Shraga-Slutz

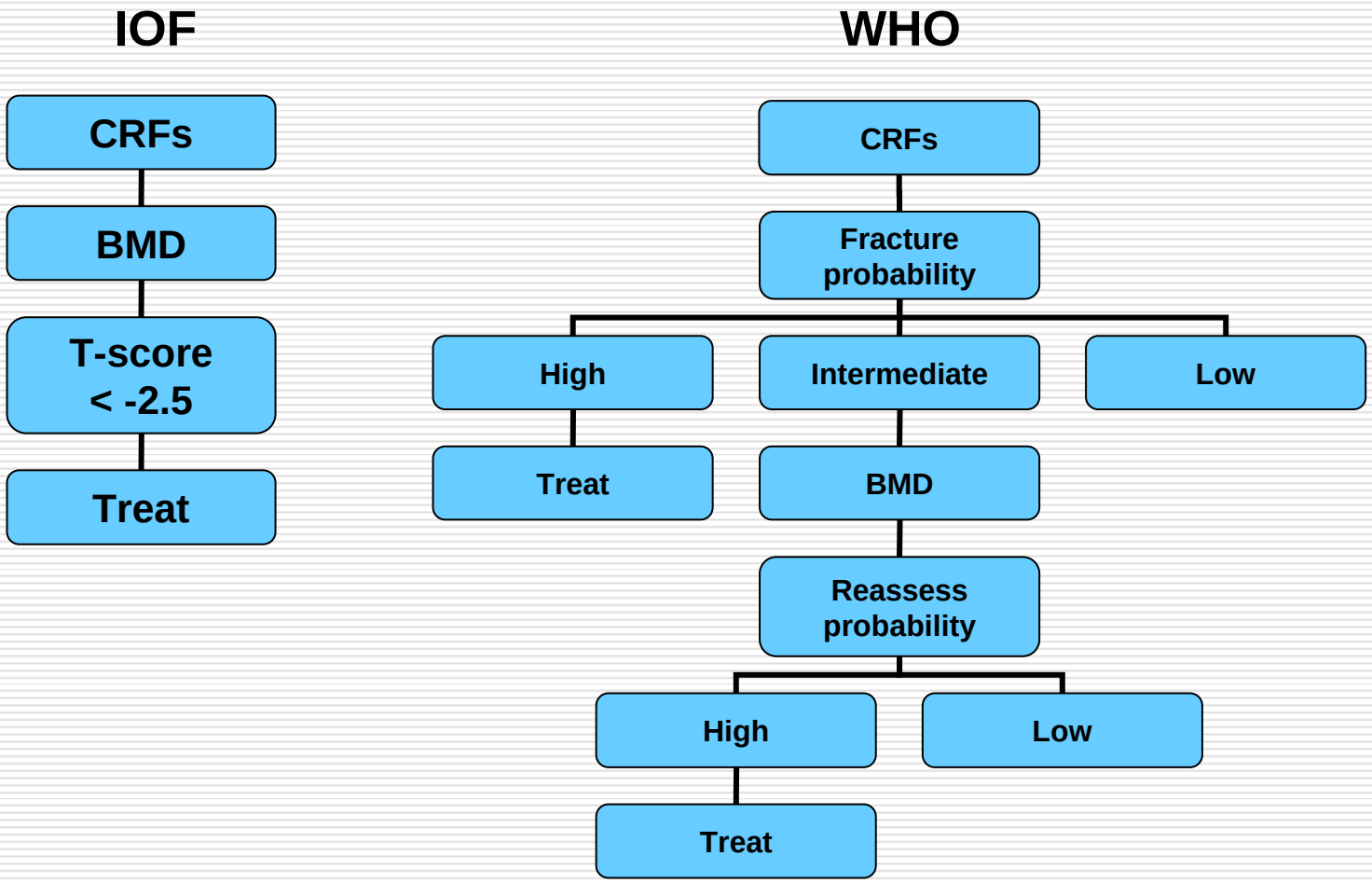
	DXA measurements	*CML*	*Controls*	*p*
Hip bone (total)	BMD, g/cm²	1.08±0.2	0.95±0.1	0.025
	T-score	0.07±1.42	-0.82±0.83	
	Z-score	0.46±1.37	-0.26±0.85	
Lumbar spine (L1-4)	BMD, g/cm²	1.27±0.22	1.12±0.15	0.029
	T-score	0.38±1.77	-0.82±1.23	
	Z-score	0.57±1.72	-0.36±1.29	
	pQCT-measurements			
Radius	Trabecular vBMD*, mg/cm³	190.9±34·2	193.9±28.8	ns
	Cortical vBMD**, mg/cm³	1211.3±23.8	1181.1±38.7	0.01
	Cortical area**, mm²	95.1±16·3	88.6±18.7	ns
Tibia	Trabecular vBMD*, mg/cm³	240.2±47.3	226.2±23.9	ns
	Cortical vBMD*, mg/cm³	1185.6±23.5	1159.4±36.2	0.017
	Cortical area**, mm²	262.6±50.7	261.3±44.4	ns

*The BMD was evaluated using two different techniques. The first was a two-dimensional measurement of the hip and lumbar spine bones using DXA. The second technique, pQCT, measures the volumetric BMD (vBMD) of the radius and tibia bones, and can separately analyze the cortical and trabecular bone compartments. DXA: the T-score is the number of standard deviations above or below the average for a young adult (20-40 years; same race and gender) at peak bone density. The reference material was from The Third National Health and Nutrition Examination Survey (NHANES III). The Z-score is the number of standard deviations above or below an average person of the same age, race and gender (reference material provided by GE Lunar Corp., Madison, WI). pQCT: vBMD and cross sectional area were measured at *4% and **25% bone length in the proximal direction. The results are given as mean ± SD.*

http://www.shef.ac.uk/FRAX/

- Assessment of osteoporosis at the primary health care level, authored by Prof. Kanis et al., was released on February 21, 2008. It is a technical report based on epidemiological and health economic analyses of population-based cohorts worldwide (10 prospective population –based cohorts with 25,000 person-years)

Comparison of European and WHO strategies for the identification of women at risk of hip fracture



Osteoporos Int, 2007

Hip fractures identified and costs of identification

Age	DXA tests /1000	High risk women identified /1000		Hip fractures expected*		Cost/identified hip fracture (£)	
		IOF	WHO	IOF	WHO	IOF	WHO
50	450	26	41	<1	1	60,823	21,940
60	450	52	65	2	4	12,930	7,566
70	500	120	355	16	30	1,731	1,069
80	550	235	606	51	91	608	424

*in women at high risk

Conclusions

- Compared to the IOF strategy, the WHO approach
  - identifies more patients at high risk of hip fracture
  - makes more effective use of BMD tests.

- At each age, the cost of the identification strategy per detected hip fracture is lower with the WHO approach.

מקרים לדיון

1. גבר בן 68, ממוצא סורי , הופנה בשל שבר L1 סימפטומטי בנפילה מגובה גוף .

- Spine Tsc -2.6 Femoral Neck Tsc -1.8
- ברקע: יל"ד, סכרת , ניתוח TURP עקב שאת הערמונית עם טיפול אגיובנטי -2000
- אם- שבר בצוואר הירך
- עישון כבד עד 2005
- Glucophage*3 Gluben *3 Rossini 4 mg Enalapril Normiten Simvastatin Aspirin

- צריכת סידן 400 מ"ג /יום , ללא פעילות גופנית מסודרת
- מעבדה:

Ca 9.0 mg/dl

Alb 4.3

Hba1C 9.2%

Ca-U 103 mg/day

25-OH-D 52 nmol/l

TSH 1.8

Testosterone 9.0 nmol/l

Male Osteoporosis Epidemiology

- According to the WHO: the prevalence - **6%** for osteoporosis
  47% for osteopenia
- A **60** y.o man has **25%** chance of sustaining an osteoporotic fracture
- By age 90 **1/6** of men will have a **hip** fracture .
- The mortality associated with hip fractures is **higher** in men than in women(**20.7%** vs **7.5 %** in women)
- The prevalence of **vertebral** or hip fracture in older men is **1/3** in women (**5-6%** vs. 16-18%)
- The prevalence of **Colles'** fracture **1/6** in women (2.5% vs. 16%)
- Men are less likely to be evaluated or receive therapy: **7%** of osteoporotic subjects,**16%** after a hip/vertebral fracture!–

Osteoporosis Int 2005

What is the relationship between fracture risk and BMD in men?

MrOS study (prospective, longitudinal, 5995 men >65 years)
Hip BMD/ hip fracture RR 3.2-fold vs 2.1-fold increase risk per SD decrease in BMD in males vs females

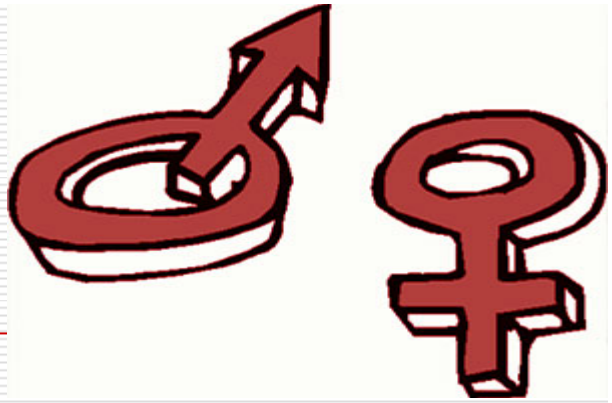
- the **Rotterdam study** : men >55 years showed absolute BMD/ risk of hip fracture was similar to women
- **A meta-analysis of cohort studies**, *JBMR 2005* : the similar conclusion

For every SD deviation reduction in BMD , men have the same fold-increase in risk as women. The number of fractures is fewer since fracture incidence is less

Clinician's Guide to the Prevention and Treatment of Osteoporosis, NOF,2008

- Addresses men age 50 and older, African-American , Asian, Latina postmenopausal women
- Applies FRAX algorithm
- Men >50 with a Tsc<-2.5, or a prior hip or spine fracture should be treated
- Patients with low bone mass (Tsc 1.0-2.5) should be treated when there is a 10-year probability of hip fracture ≥ 3% or a 10- year probability of a major osteoporosis-related fracture ≥20 %

Sexual differences



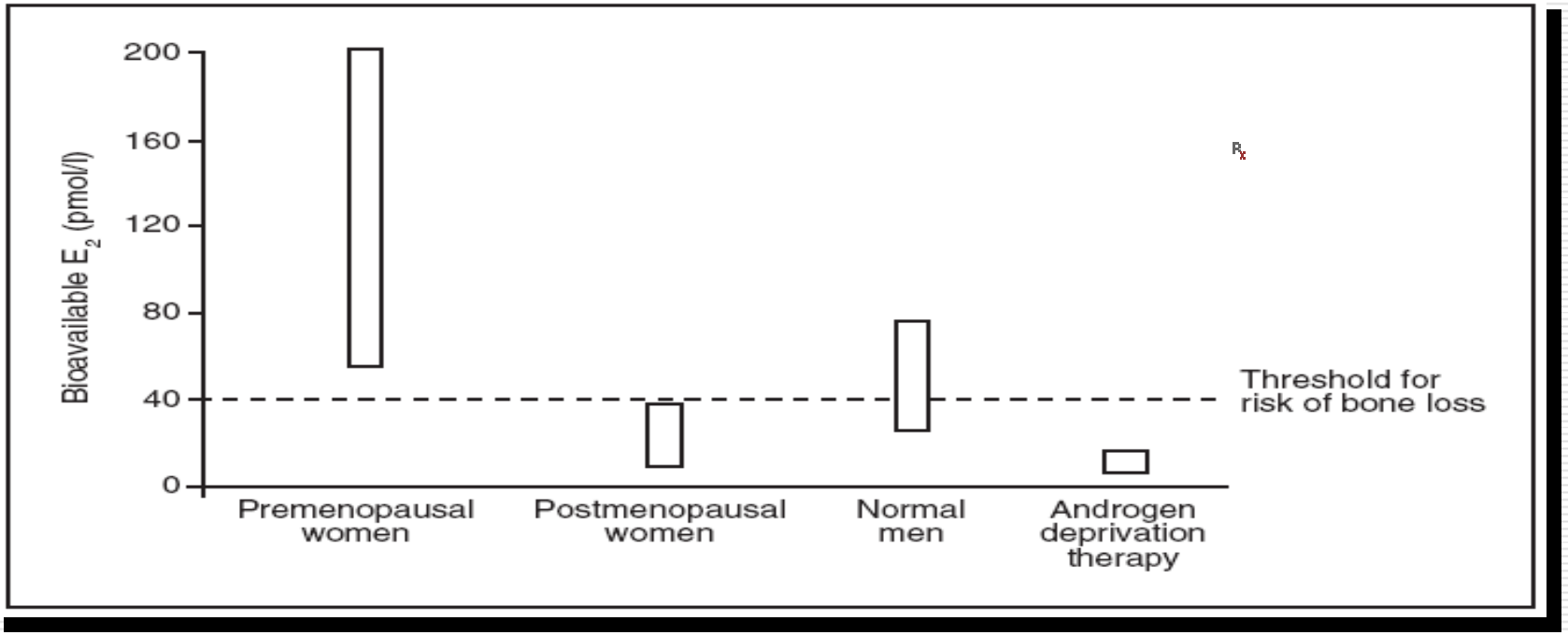
- 8-10% more peak bone mass
- Lack a menopausal equivalent - lower rates of bone loss. Bone loss is by trabecular thinning vs trabecular perforation
- Enhanced periosteal bone formation→ a greater cross-sectional bone diameter
- Shorter life expectancy

Major role of estrogen

- The animal models of E deficiency knockout of both the ά-estrogen receptor and the aromatase gene in mice : lower BMD.
- Case-reports of a man with E resistance d/t an inactivating mutation in the ά-estrogen receptor gene & in 4 adult man with aromatase deficiency: transdermal E for 14 months resulted in BMD ↑25-37% from baseline. The lack of efficacy of alendronate.
- Boys with E excess d/t gain-of-function mutations of the aromatase gene – short stature d/t precocious epiphyseal closure and ↑ BMD.
- The administration of a high dose of E to male-to-female transsexuals ↑ BMD at lumbar and femoral sites

Endocrine Rev, 2003

Estradiol Levels in Normal and Hypogonadal Individuals

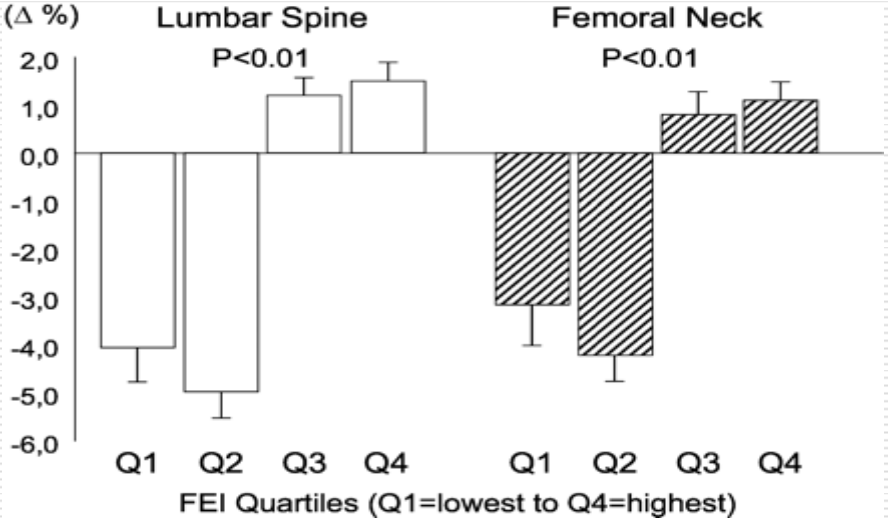


Lipton A. Oncologist 2004;9(Suppl 4):38

Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men

JCEM, 2003

200 men, 55-88 years, for 4 years



E/T in normal men>E/T in osteoporotic (p<0.01)

Testosterone replacement

- A meta-analysis of placebo-controlled trials of testosterone treatment in hypogonadal men - a beneficial effect on lumbar spine BMD, but equivocal at FN (intramuscular testosterone!)

The effect of fracture risk is unknown

Bone Loss During Initial ADT for Prostate Cancer

Table 2 Bone loss during initial androgen-deprivation therapy for prostate cancer.

Study	Number of patients	Hormone therapy	Change in BMD at 1 year	
			Hip	Spine
Eriksson *et al.* (1995)[45]	11	Orchiectomies	–9.6%	ND
Maillefert *et al.* (1999)[27]	12	GnRH agonist	–3.9%	–4.6%
Daniell *et al.* (2000)[28]	26	Orchiectomies or GnRH agonist	–2.4% to –3.7%	ND
Smith *et al.* (2001)[29]	47	GnRH agonist	–3.3%	–1.8%
Berutti *et al.* (2002)[30]	35	GnRH agonist	–2.3%	–0.6%
Smith *et al.* (2003)[31]	106	Orchiectomies or GnRH agonist	–2.1%	–2.8%

BMD, bone mineral density; GnRH, gonadotropin-releasing hormone; ND, not done.

Normal men lose BMD at a rate ≈ 0.5-1 %yearly

Postmenopausal women lose BMD at a rate ≈ 2-3% yearly for 5 years

J Eastham, J Urology, 2007

J Clin oncol, 2005- retrospective , 3887 men on GnRh vs 7774 men without GnRH- RR 1.45 VF, 1.35 HF

Table 4. Estimated Number Needed to Harm for the Occurrence of Any Fracture within 12 to 60 Months after Diagnosis, According to Age and Extent of Androgen Deprivation.*

Age	Gonadotropin-Releasing Hormone Agonist			Orchiectomy
	1–4 doses	5–8 doses	≥9 doses	
	no. needed to harm (95% CI)			
66–69 yr	74 (50–146)	42 (29–73)	18 (16–24)	15 (13–18)
70–74 yr	69 (46–146)	39 (27–71)	17 (15–20)	14 (12–17)
75–79 yr	61 (41–125)	34 (24–61)	15 (14–17)	13 (11–15)
≥80 yr	46 (32–91)	26 (19–45)	12 (11–13)	10 (9–11)

* Estimates were calculated on the basis of adjusted rates of fracture five years after diagnosis from a Cox model with any fracture as the outcome. Doses of a gonadotropin-releasing hormone agonist were grouped according to the number of doses received within the 12 months after diagnosis. CI denotes confidence interval.

Shahinian, V. et al. N EJM, 2005- 50, 613 men with PC , 1992-1997

The NEW ENGLAND JOURNAL of MEDICINE

RCT to prevent bone loss in GnRh agonist-treated men with prostate cancer

Table 2. Randomized controlled trials to prevent bone loss in GnRH agonist–treated men with prostate cancer

Study	*n*	Arms	Results	Treatment effect at 12 mo (95% CI)
Smith et al. (7)	47	Pamidronate vs no pamidronate	Pamidronate increased BMD of hip and spine	Lumbar spine: 3.8% (1.8-5.7%) Total hip: 2.0% (0.7-3.4%)
Diamond et al. (37)	21	Pamidronate vs placebo	Pamidronate increased BMD of hip and spine	Not reported
Smith et al. (22)	106	Zoledronic acid vs placebo	Zoledronic acid increased BMD of hip and spine	Lumbar spine: 7.3% (5.3-8.8%) Total hip: 3.9% (2.4-5.0%)
Smith et al. (23)	48	Raloxifene vs no raloxifene	Raloxifene increase BMD of hip	Lumbar spine: 2.0% (−0.2-4.0%) Total hip: 3.7% (2.0-5.4%)
Steiner (44)	46	Toremifene vs placebo	Toremifene increased BMD of hip and spine	Not reported

M.Smith, Clin Cancer Res, 2006

Greenspan S, n=112, **ALN** 70 mg vs placebo Spine : 5% difference, hip:2.3 %

Ann Intern Med, 2007

Denosumab, ongoing Phase III, 1,468 men. Outcomes- vertebral fractures,BMD

Toremifene,ongoing Phase III, 1,335 men, Outcomes- veretebral fractures, BMD

I.Shraga-Slutzky, 2008

מקרה שני

אישה בת 55 , פונה בשל Ca- 10.7 mg/dl שנמצא בבדיקה שגרתית . מרגישה טוב. שוללת אבני כליות, שברים .

- לא ידוע על הפרעה במשק הסידן במשפחה
- ברקע: בריאה בד"כ , ללא טיפול תרופתי קבוע
- מנופאוזה מגיל 52 , ללא HRT

מעבדה-

Ca – 10.4-10.8 from 2005

Alb – 4.0

Phos – 3.0

25-OH-D – 50 nmol/l

Ca-U 270 mg/dl

Spine Tsc -2.3 FN -2.2 Rad 1/3 -2.7

PHPT and fractures risk

- ***Khosla, JBMR, 1999-*** **population-based cohort of 407 cases of primary HPT (93 men and 314 women) recognized during 1965-1992**
- 471 fractures / 5766 person-years
- Overall fracture risk - SIR 1.3, 95% [CI] 1.1-1.5).
- vertebral fractures-SIR 3.2, 95% CI 2.5-4.0
- distal forearm fractures -SIR 2.2, 95% CI 1.6-2.9
- rib -SIR 2.7, 95% CI 2.1-3.5
- pelvic fractures -SIR 2.1, 95% CI 1.1-3.5
- femur fractures -SIR 1.4, 95% CI 1.0-2.0.

Surgery or Surveillance for Mild Asymptomatic Primary Hyperparathyroidism

- 25% incidence of progressive disease over 10-yr period
- RCT, 2004- benefit of PTx on BMD, quality of life, psychological symptoms
- RCT, *JCEM, 2007-*

PTx n=13 vs no-PTx n=16

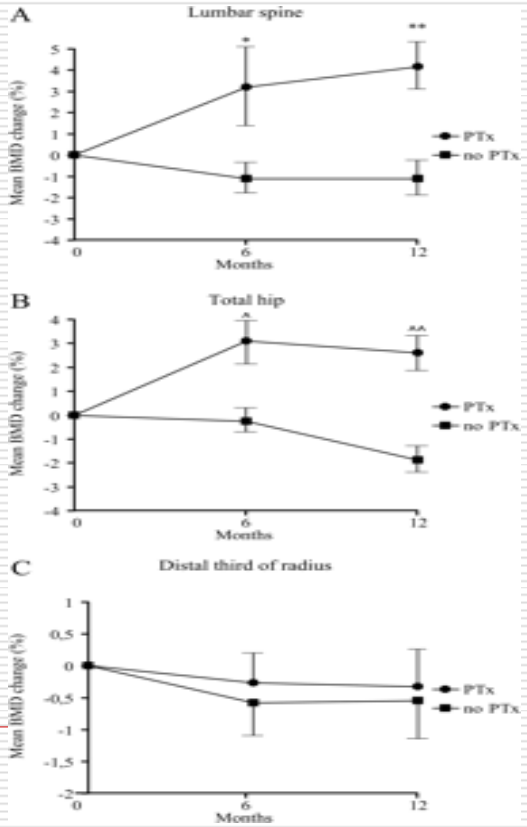
1-year follow –up

1/16- renal stone

1/16- VF

3/16- Ca-U>400 mg/day

The patients with the lowest Tsc showed the greatest Increment in the spine BMD



I.Shraga-Slutzky, 2008

Bisphosphonates in asymptomatic PHPT

- 2 RCT: 1. 1-year – BMD difference as 5 % at the spine and FN
  significant reduction in bone turnover markers
  decrease in Ca level by 0.34

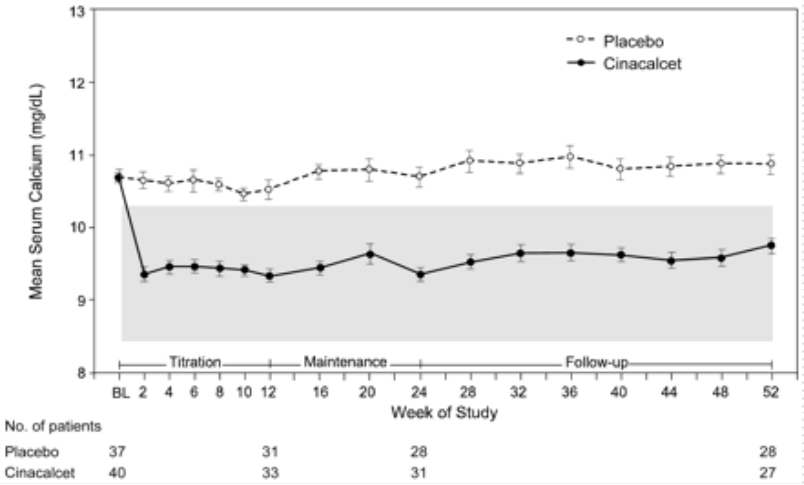
  2. 2-year- BMD difference as 6.8 % at the spine and 3.6% FN
  significant reduction in bone turnover markers
  no Ca change

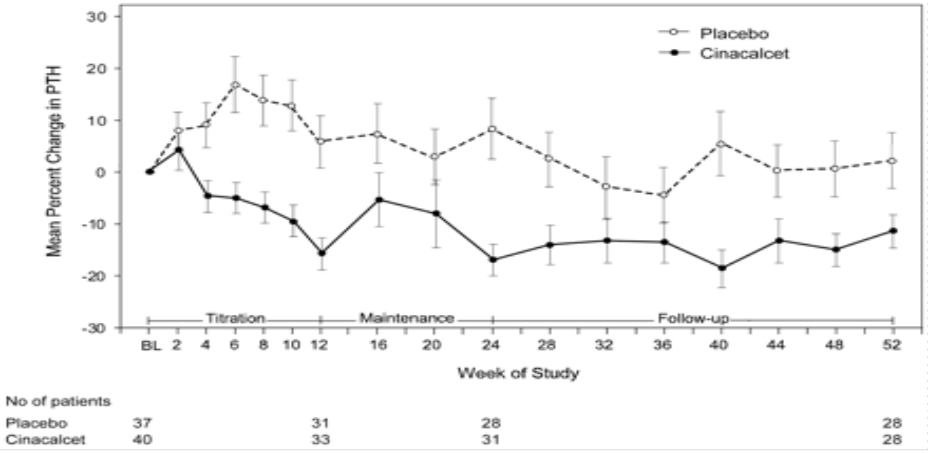
Cinecalcet in PHPT

- *Peacock , JCEM, 2005-*

52-weeks RCT , Cinecalcet n=40, placebo n=38

At baseline mean Ca=10.7 mg/dl mean PTH=105 pg/ml





BMD was unchanged, but bone turnover markers significantly increased .

These effects were maintained over 5 years of therapy in an open-label extension study *(JBMR,2006)*