

Current Concepts in Fracture Prevention

Bess Dawson-Hughes, M.D.

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Surgeon General's Report October 13, 2004

"Osteoporosis isn't just your grandmother's disease."

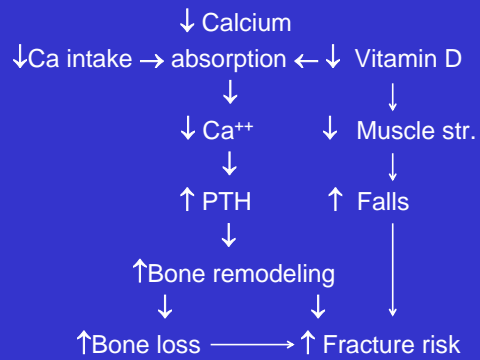
By 2020, half of all Americans over age 50 will have or be at risk for osteoporosis.

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Objectives – Fracture Prevention

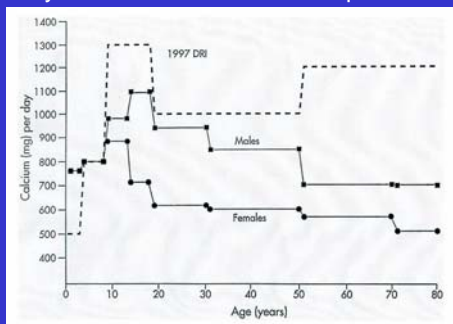
- Non-pharmacologic strategies
 - Diet
 - Exercise
 - Hip protectors
- Pharmacologic strategies
 - Patient selection
 - Treatments- efficacy, tolerability

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Mean Calcium Intakes Compared to NAS Dietary Reference Intakes – Adequate Intakes



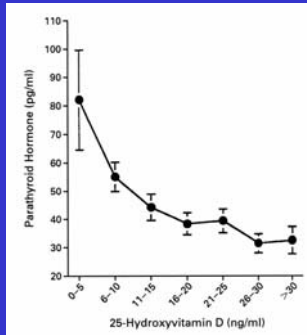
Bryant R.J. J Am Col Nutr 1999; 18: 406S.

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Vitamin D Requirement- Endpoints to Consider

- PTH suppression
- BMD
- Physical performance
- Falls
- Fractures

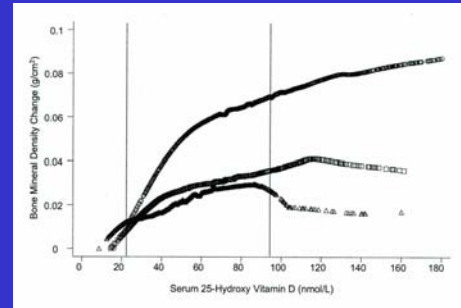
6



Thomas MK. *N Eng J Med* 1998; 338: 777-83.

7

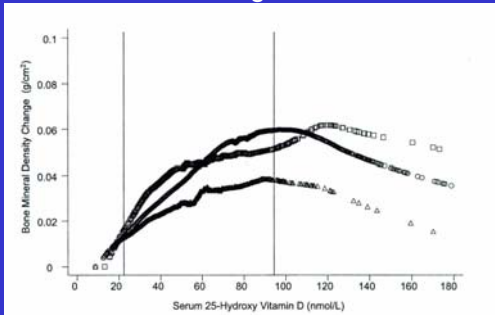
HANES III – Serum 25(OH)D and Total Hip BMD Adults Age 20 – 49 years



Bischoff-Ferrari HA. *Am J Med* 2004; 116: 634-9.

8

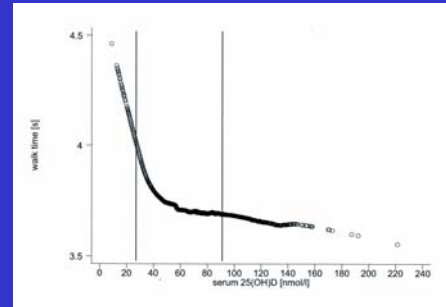
HANES III – Serum 25(OH)D and Total Hip BMD Adults Age 50 +



Bischoff-Ferrari HA. *Am J Med* 2004; 116: 634-9.

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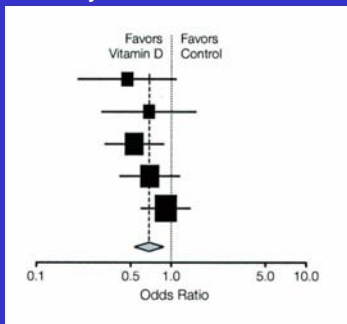
HANES III – Serum 25(OH)D and Walk Time



Bischoff-Ferrari HA. *Am J Clin Nutr* 2004;80:108-13.

10

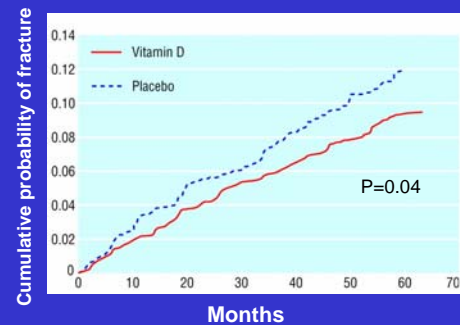
Meta-Analysis of Vitamin D and Falls



Bischoff-Ferrari HA. *JAMA* 2004; 291: 1999-2006.

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Cumulative Incidence of Any First Fracture



Trivedi DP, et al. *BMJ* 2003; 326: 469.

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Opinions on Optimal 25(OH)D Levels and Doses of Vitamin D₃ Needed to Achieve These Levels

Participant	Optimal 25(OH)D (nmol/L)	Oral Vit D ₃ dose needed* (IU/d)
Lips	50	400-600
Holick	75	1000
Heaney	80	1600
Meunier	75	800
Vieth	70	1000
D-Hughes	80	1000

*Estimated average requirement for optimal 25(OH)D level 13

Intake Recommendations for Men and Women National Academy of Sciences

Age yrs	Calcium mg/d	Vitamin D UI/d
30-50	1000	200
51-70	1200	400
71+	1200	600

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Vitamin K

- Vitamin K is required for the formation of osteocalcin
- Osteocalcin is the most abundant non-collagenous protein in bone matrix
- Osteocalcin acts as a regulator of bone mineralization
- In vitamin K deficiency, undercarboxylated osteocalcin is produced
- Undercarboxylated osteocalcin may not function normally

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Vitamin K Intake and Hip Fractures Framingham Study 1988-1995 (888 subjects, 44 hip fractures)

Q	Median vit K intake mcg/d	RR hip fracture	CI
1	56	1.0	
2	105	0.53	0.22, 1.28
3	156	0.59	0.25, 1.39
4	254	0.35	0.13, 0.94

P for trend = 0.047

Booth SL, et al. *Am J Clin Nutr* 2000; 71: 1201-8.

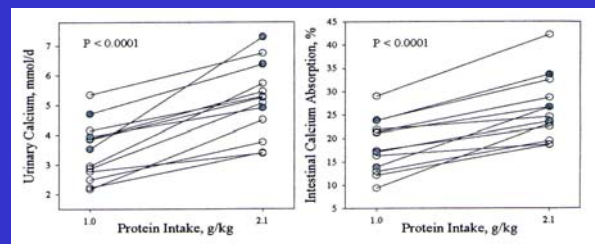
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Effects of Protein on Calcium Homeostasis

- Increases urine calcium losses
- Promotes intestinal calcium absorption
- Stimulates production of IGF-1 and perhaps other bone growth factors

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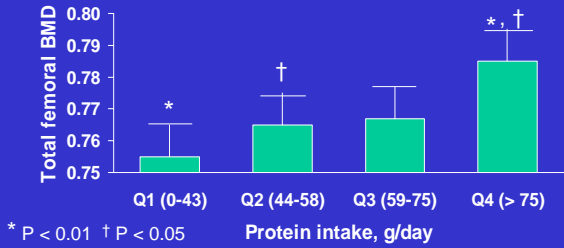
Urine calcium excretion and fractional calcium absorption in 13 healthy women on low and high protein intakes



Kerstetter. *JCEM* 2005; 90(1):26-31

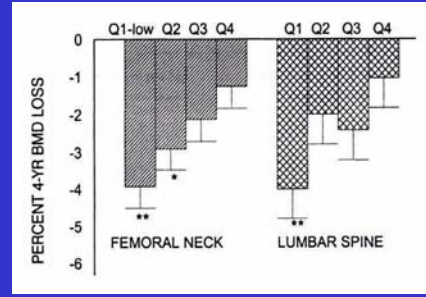
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Protein Intake and Total Hip BMD in Caucasian Women (NHANES III)



* P < 0.01 † P < 0.05
 Kerstetter JE. *Calcif Tissue Int* 2000; 66: 313. 19

Protein Intake and Rates of Bone Loss in Elderly Men and Women



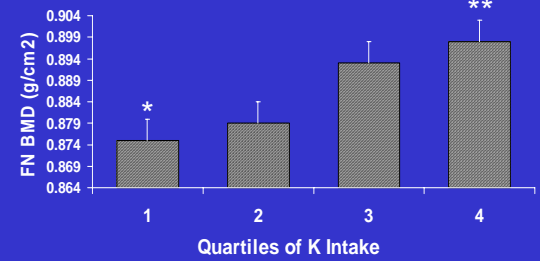
Hannan MT. *J Bone Miner* 2000; 15: 2504-12. 20

Acid-base Balance and Bone Health

- Acid sources – protein, cereal grains
- Alkali sources – fruits and vegetables (these foods are also rich in potassium and magnesium)
- The skeleton buffers an acid load and in the process promotes bone resorption and impairs bone formation (Bushinski, U Rochester)

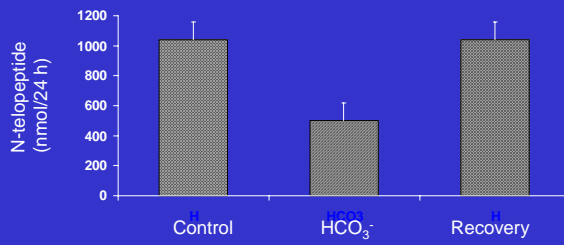
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Association of Potassium Intake with BMD in Postmenopausal Women



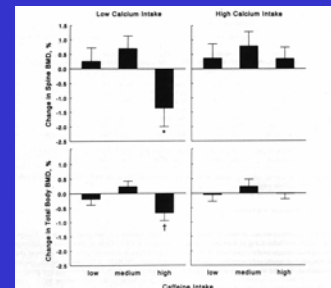
New SA. *Am J Clin Nutr* 1997;65:1831-9. 22

Acute Impact of HCO₃⁻ (90 mmol/d) on Bone Resorption in Healthy Young Men

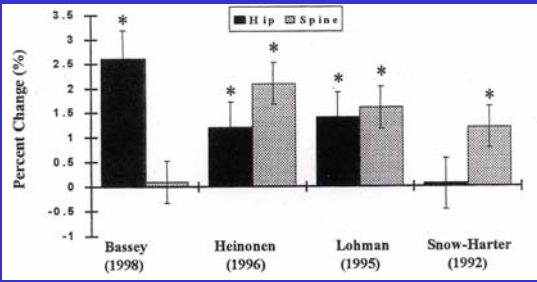


Maurer M. *Am J Physiol Renal Physiol* 2003; 284: F32-F40. 23

Caffeine and Bone Loss in Postmenopausal Women



Harris S, Dawson-Hughes B. *Am J Clin Nutr*, 1994; 60:573-8. 24



Bassey EJ, et al. *J Bone Miner Res* 1998; 13: 1805-13.
 Heinonen A, et al. *Lancet* 1996; 348: 1343-47.
 Lohman T, et al. *J Bone Miner Res* 1995; 10: 1015.
 Snow-Harter C, et al. *Bone Miner Res* 1992; 7: 761-9.

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Home Exercise Program (233 ambulatory women, age 80+ years; 1-year duration)

- 4 home training visits in first 2 months
- Program - 30 minutes at least 3 times/week
- Aims - strength, balance
- Outcome - falls
- Monthly falls diary

Campbell AJ, et al. *BMJ* 1997; 315: 1065-9.

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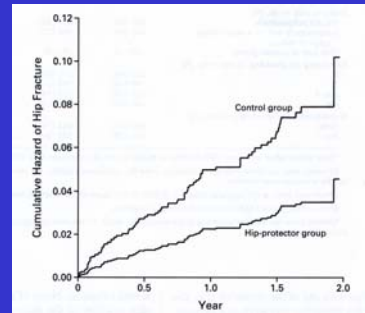
Home Exercise Program Results

- For first fall in exercise group compared with controls, RR= 0.61 (0.39 – 0.97)
- Total # of falls – 152 in control group
88 in exercise group

Campbell AJ, et al. *BMJ* 1997; 315: 1065-9.

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Hip Protectors Lower Hip Fractures in 1800 Frail Elderly Subjects



Kannus P. *N Eng J Med* 2000; 343: 1506-13.

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WHO Definition of Osteoporosis Based on Bone Mass Measurement at Any Site

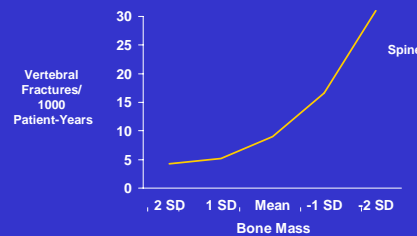
Classification	T-score*
Normal	above -1
Osteopenia	-1.0 to -2.5
Osteoporosis	-2.5 and below

*T-score = Standard deviation of the mean for young adult white women

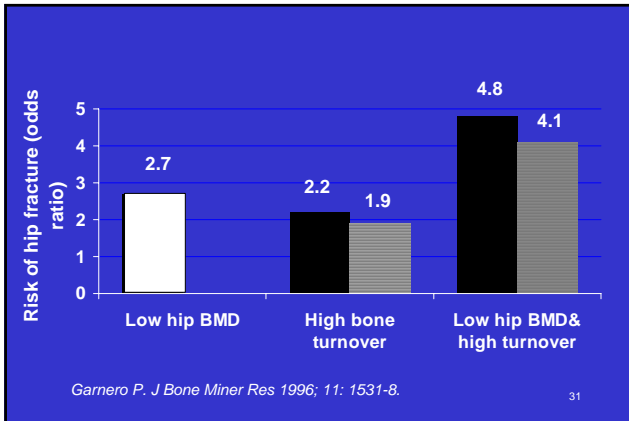
Kanis JA. *Osteoporos Int* 1994; 4: 368-81.

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Low BMD Is Strongly Associated With Increased Fracture Risk



Adapted from Miller PD et al. *Semin Arthritis Rheum.* 1996;25:361-372.
 Wasnich RD et al. *J Nucl Med.* 1989;30:1166-1171.



NOF Guide: Postmenopausal Women - Who Should Be Treated?

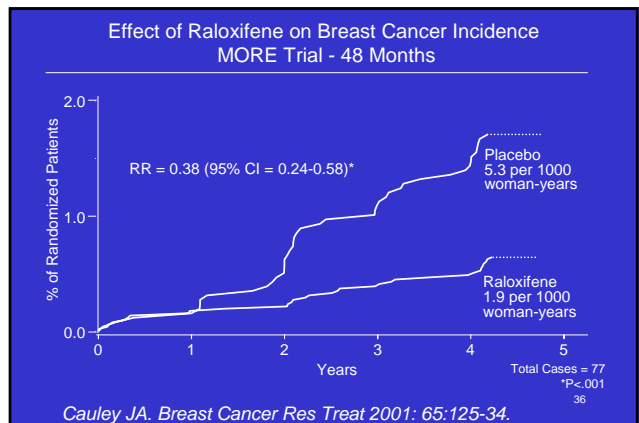
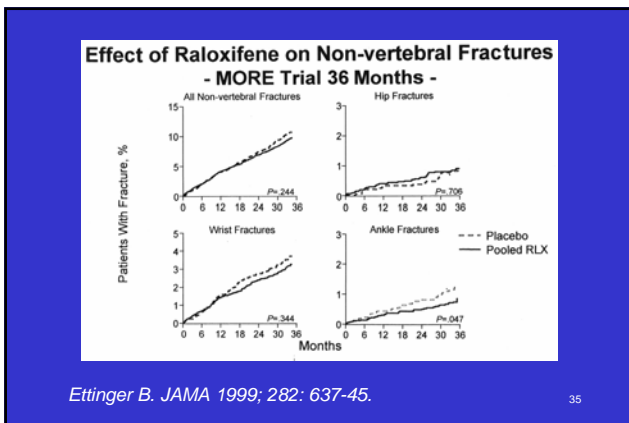
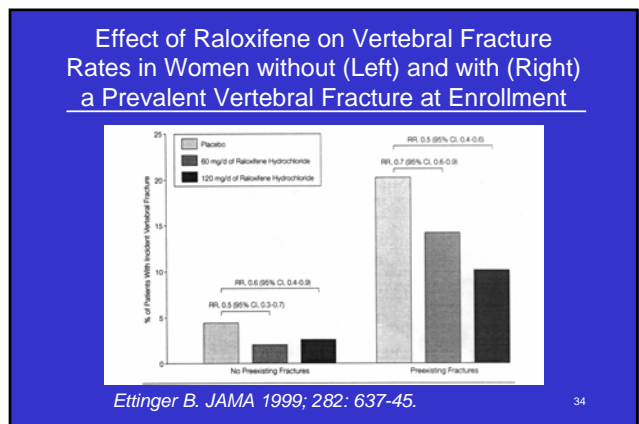
- Up to age 65
 - if one risk factor, measure bone density
 - treat if T-score -1.5 or below
- Age 65
 - assess risk factors and measure bone density
 - if no risk factor and T score -2.0 or below, treat
 - if risk factor(s) and T score -1.5 or below, treat
- All women with vertebral or hip fracture - treat

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FDA-approved Drugs for Prevention and/or Treatment of Osteoporosis

- Raloxifene
- Calcitonin
- Alendronate
- Risedronate
- PTH 1-34

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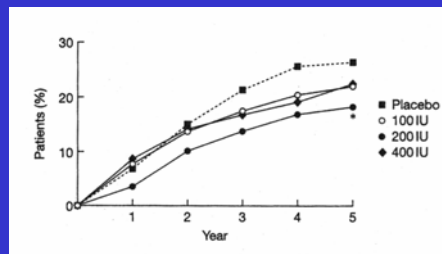


Nasal Calcitonin Intervention Trial

- Osteoporotic women , mean age 68, n = 1,255
- Groups:
 - Placebo
 - CT 100 IU
 - 200 IU
 - 400 IU
- All women received 1,000 mg Ca and 400 IU vit D
- Duration: 5 years
- Outcome: new vertebral fractures

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Nasal Calcitonin and Cumulative Incidence of Vertebral Fractures



Chesnut et al. Am J Med 2000; 109: 267-76.

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Fracture Intervention Trial FIT:

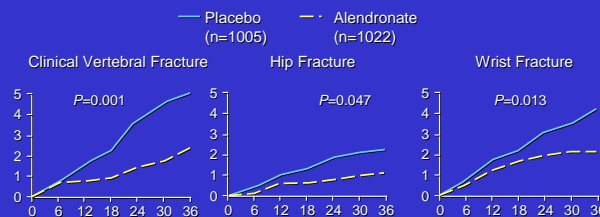
(Placebo, Alendronate 5 mg/d x 2 yrs, then 10 mg/d)

	FIT-1	FIT-2
Subjects (n)	2027	4432
Study duration (years)	3	3
Spine T-score(Nhanes)	-2.3	-2.0 (-1.6)
Prevalent fractures	100%	0%
Age (years)	71	68

Black DM et al. Lancet. 1996;348:1535.
Cummings SR et al. JAMA. 1998;280:2077.

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Effect of Alendronate on Fracture Risk in Women With Existing Vertebral Fractures



Black et al. Lancet. 1996;348:1535-1541.

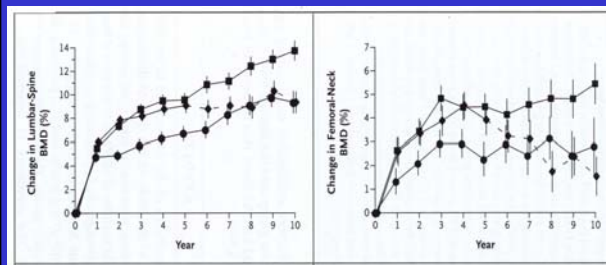
Risk of Clinical Fractures in Patients without Prevalent Vertebral Fractures Fit II

	Placebo	Alendronate	RR
T-score	N(%)	N(%)	(95% CI)
< -2.5	159 (19.6)	107 (13.1)	0.64 (0.50-0.82)
-2.5 to -2.0	87 (12.3)	92 (12.7)	1.03 (0.77-1.39)
-2.0 to -1.6	66 (9.5)	73 (10.9)	1.14 (0.82-1.60)

Cummings et al. JAMA 1998; 280: 2077-82.

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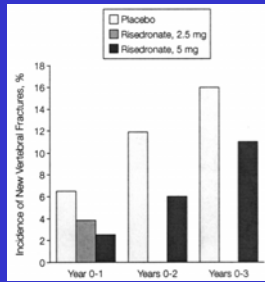
Alendronate – 10-years



Bone HG, et al. N Engl J Med 2004; 350: 1189-99.

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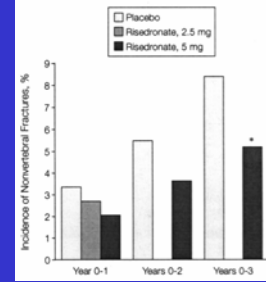
Effect of Risedronate on Incidence of Vertebral Fractures



Harris et al. JAMA 1999; 282:1344-52.

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Effect of Risedronate on Incidence of Non-vertebral Fractures

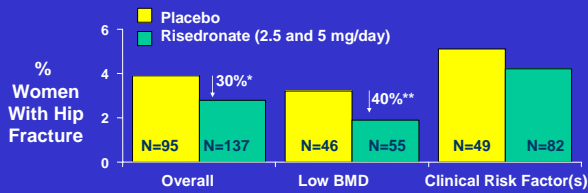


Harris et al. JAMA 1999; 282:1344-52.

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Risedronate: Hip Fracture Reduction

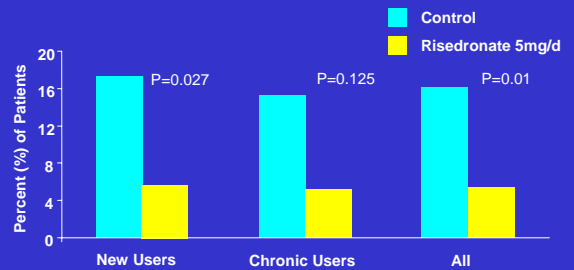
9331 women with PMO and/or nonskeletal risk factor(s) treated for 3 years



Relative risk reduction: *McClung MR et al. N Engl J Med. 2001;344:333-340.*
 *P=0.02 vs placebo; **P=0.009 vs placebo.
 N = number of women with new fracture.

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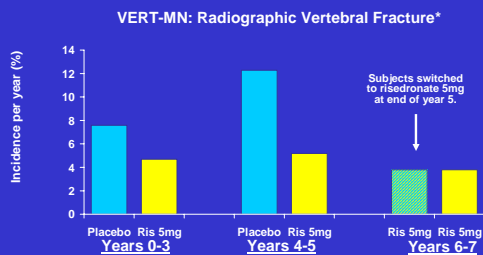
Effect of Risedronate on Vertebral Fracture Incidence in Steroid-induced Osteoporosis



Wallach S. Calcif Tissue Int 2000; 67: 277-85.

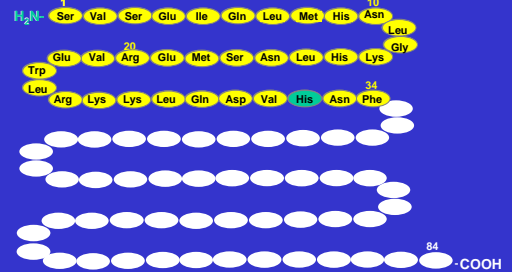
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Annualized Incidence of Subjects Experiencing Any New Vertebral Fracture Over Years 0-3, 4-5 or 6-7

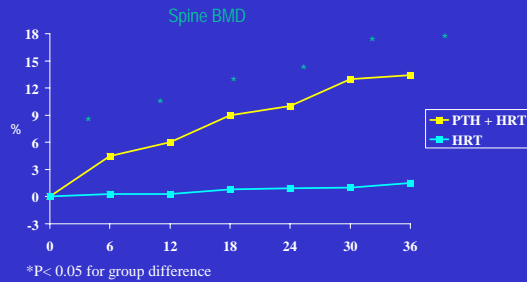


* Annualized fracture incidence represents the percentage of subjects experiencing any new vertebral fracture divided by the number of years in the observed interval. *Sorensen, et al, ISCD abstract, 2/03 annual meeting.*

Human Parathyroid Hormone 1-34 and 1-84



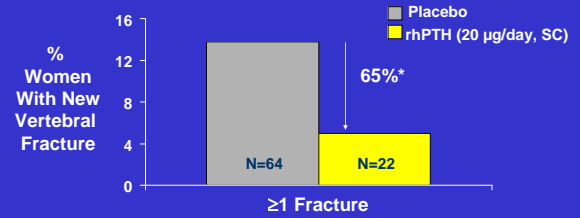
Change in BMD with hPTH + HRT or HRT Alone in Postmenopausal Osteoporosis



Cosman F, et al. *J Bone Miner Res* 2001;16:925-931.

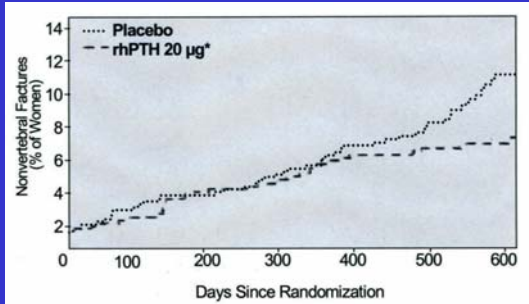
rhPTH (teriparatide): Vertebral Fracture Reduction

1637 postmenopausal women with vertebral fracture treated for a mean period of 18 months



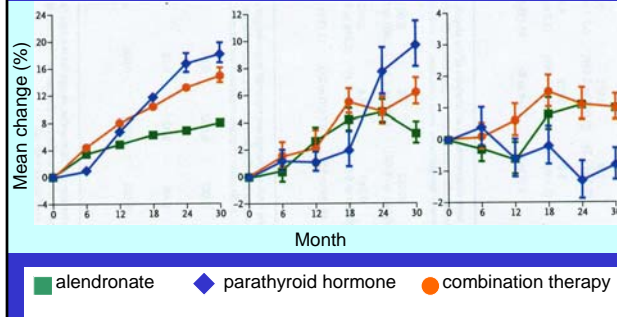
*Relative risk reduction, $P \leq 0.001$ vs placebo. N = number of women with new fracture. Neer RM et al. *N Engl J Med*. 2001;344:1434-1441.

Effect of PTH (1-34) on Risk of Nonvertebral Fractures in Postmenopausal Women



Neer RM. *N Engl J Med* 2001; 344:1434-1441.

Spine, Femoral neck, Radial shaft



Finklestein JS. *N Engl J Med* 2003; 349: 1216-26.

Conclusions

- Osteoporosis is
 - easily diagnosed
 - under treated
- Effective treatments are available

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Dr. Dawson-Hughes – Q & A

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