

**ENDOCRINOLOGY FOR THE PRIMARY CARE  
PHYSICIAN—'PEARLS'**



**'ENDOCRINE PEARLS-2008'**

- What's new in the diagnosis of osteoporosis?
- Bisphosphonates and ONJ
- Subclinical thyroid disease- Rx or no Rx
  - Subclinical hypothyroidism
  - Subclinical hyperthyroidism

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## OSTEOPOROSIS DIAGNOSIS

- Based on BONE MINERAL DENSITY assessment
  - Normal--T > -1.0
  - Osteopenic-- T = -1.0 to -2.5
  - Osteoporosis-- T < -2.5

T Score--patient compared to cohort of NORMAL YOUNG women at maximum bone mass

Z Score--patient compared to cohort of AGE MATCHED women

## NOF GUIDELINES: Initiating Therapy

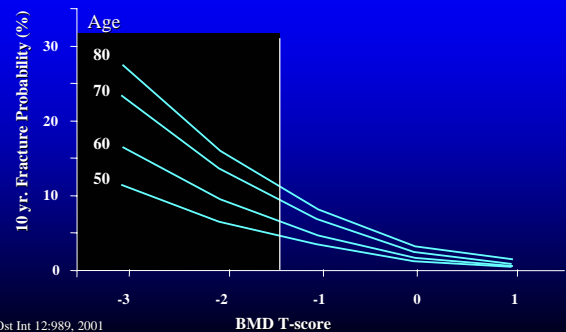
- Initiate therapy if BMD T-score is:
  - Below -2.0 in absence of risk factors
  - Below -1.5 if other risk factors are present
- Initiate therapy in women over age 70 with multiple risk factors (especially those with previous non-hip, non-spine fractures) without BMD testing

National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. Belle Mead, NJ: Excerpta Medica, Inc; 1998.

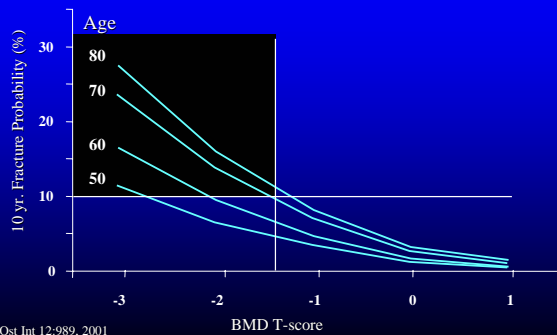
## NOF GUIDELINES: Initiating Therapy

- Initiate therapy if BMD T-score is:
  - Below -2.0 in absence of risk factors
  - Below -1.5 if other risk factors are present
- **UNKNOWN** how well these thresholds will identify who will fracture—and thus who may benefit from Rx to reduce fracture risk.

## 10 Yr. PROBABILITY OF FRACTURE



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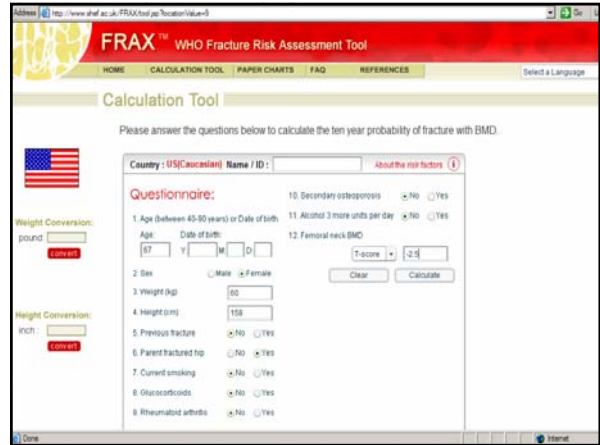
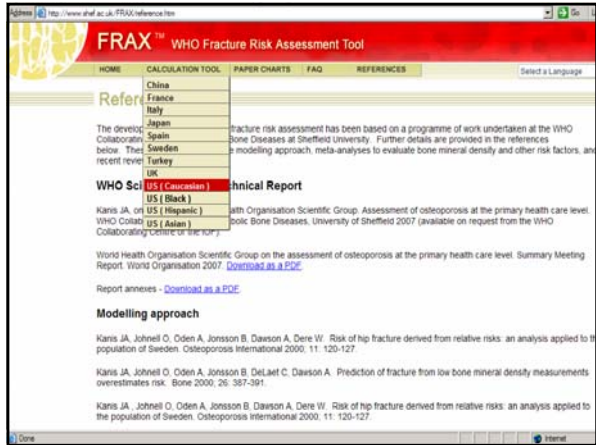
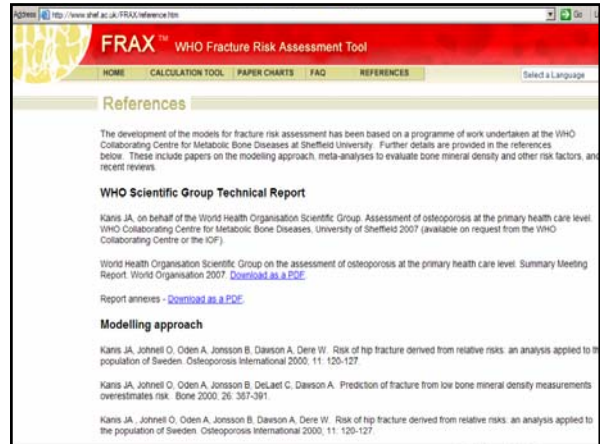


## WHO FOR OSTEOPOROSIS: AGE ADJUSTED RELATIVE RISK OF FRACTURE

- Steroid use---2.3
  - Family Hx hip fracture---2.3
  - Hx prior fracture---2.1
  - BMI---2.0
  - R.A.---1.7
  - Alcohol/Smoking---1.6
- } Weighted appropriately to express fracture risk.  
} Population/gender specific.

[www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)

Calculates absolute fracture risk in untreated patients age 40-90



**NOF GUIDELINES 2008:**  
**WHO SHOULD BE TREATED**

Post-menopausal women and men age >50

- A hip or vertebral fracture (clinical/morphometric).
- T score < -2.5 at femoral neck, total hip or spine (after secondary causes R/O).
- **Low bone mass and 10 year FRAX risk of fracture >3% hip, >20% major osteoporotic related fracture.**

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

## FRAX SHORTCOMINGS

- Male T score and referral female T score
- DXA needs to be adjusted to NHANES data base
- Clinical fractures used rather than morphometric fracture
- Femoral neck BMD by DXA only used
- IT HAS NOT BEEN PROVEN TO REDUCE FRACTURE RATE

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## BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW

I was gratified to be able to answer promptly and I did.

I said I didn't know.

*Life on the Mississippi; Mark Twain*

## **FOSAMAX** WARNING

Fosamax has been linked to a serious bone disease known as **osteonecrosis of the jaw (ONJ)** or "dead jaw." Symptoms of ONJ include loosening of the teeth, severe infections and swelling. If you or a loved one has suffered any of the serious side effects listed above, call Phillips & Associates toll free at 1-800-706-3000 for a free consultation.

**SERIOUS INJURY LAWYERS**

**PHILLIPS**  
ASSOCIATES  
ARIZONA'S LAW FIRM

**602.258.8888**

Toll Free 1.800.706.3000

www.PhillipsLaw.com

www.fosamax-injury.com

Az Republic 7/06

## BISPHOSPHONATE EFFECTS ON BONE

- Inhibit osteoclast activity-reduce bone turnover\*\*
- LONG LASTING in bone (alendronate t1/2=12 yrs.)
- Anti tumor effects:
  - Induce tumor cell apoptosis
  - Inhibit tumor cell adhesion to bone
  - Anti angiogenesis
  - Reduce skeletal complications incl. hypercalcemia in those with myeloma/metastatic cancer to bone (breast)



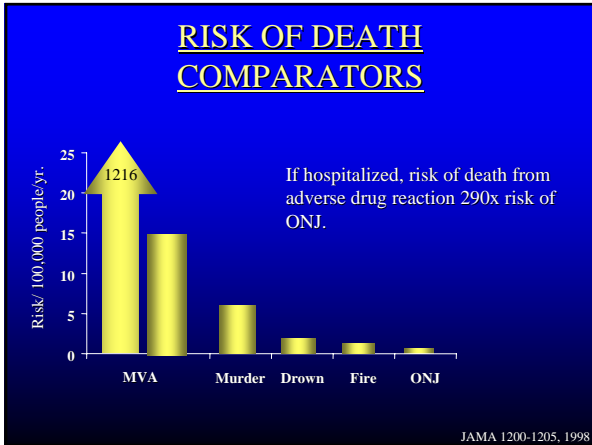
### PREVALENCE OF ONJ IN BIPHOSPHONATE Rx

- 6-10% in those with malignancy
  - Time/dose dependent
  - 94% of these had been Rx with zoledronate, pamidronate or both
    - 85% of these had myeloma or metastatic breast Ca
    - 4% had osteoporosis
- 60% of all cases occurred after major dental surgery
- **PREVALENCE OF ONJ IN THOSE ON ORAL Rx FOR OSTEOPOROSIS IS UNKNOWN**

↓

BEST 'GUESSTIMATE': 1/120,000

AIM 144:753, 2006



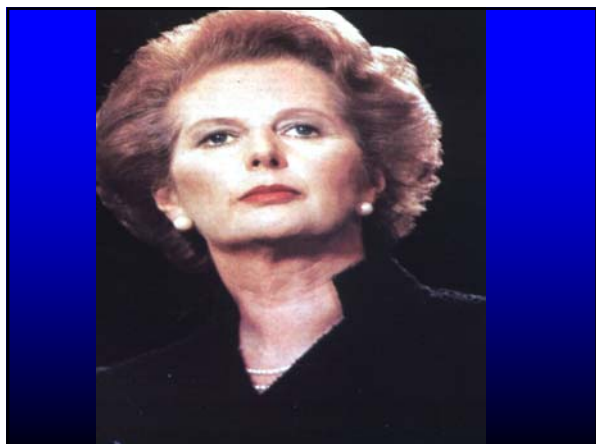
### ORAL BIPHOSPHONATES AND ONJ RECOMMENDATIONS

- Preventive strategies:
  - Undertake all major dental work prior to starting Rx
  - Remove all foci of dental infection prior to Rx
  - Treatment: pain/infection control, careful debridement of dead bone but avoid wide excision
- ADA website:  
[www.ada.org/prof/resources/topics/osteonecrosis.asp](http://www.ada.org/prof/resources/topics/osteonecrosis.asp)

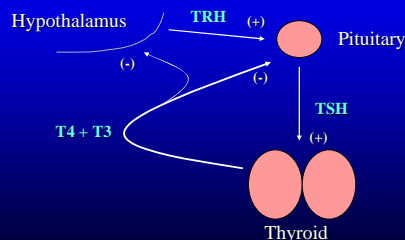
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## REGULATION OF THYROID FUNCTION

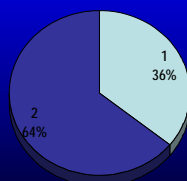


### SUBCLINICAL THYROID DISEASE WOULD YOU TREAT??

A completely asymptomatic 65 yo woman with no physical findings of note and no goiter:

TSH--6.5 (.3-5.0)  
Free T4--1.0 (.6-1.6)  
Total T4 --6.5 (5-11)

1. Yes
2. No

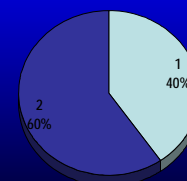


### SUBCLINICAL THYROID DISEASE WOULD YOU TREAT??

A completely asymptomatic 65 yo woman with no physical findings of note and no goiter:

TSH-- 0.08 (.3-5.0)  
Free T4-- 1.2 (.6-1.6)  
Total T4-- 7 (5-11)

1. Yes
2. No



### SUBCLINICAL HYPOTHYROIDISM

- No symptoms
- **TSH 5-10 mIU/L, normal T4/T3**
- **Potential complications**
  - Progression to overt hypothyroidism
  - Hyperlipidemia
  - Cardiovascular disease
  - Symptoms/well being
- Effect of Rx---controversial

### TSH—WHAT IS NORMAL?

NHANES III(1994); 0.4-4.0 mIU/L (mean-1.4mIU/L)

- 95% of rigorously screened normal volunteers: TSH 0.4-2.5 mIU/L
- **NO** evidence of adverse outcomes with TSH of 2.6-4 mIU/L
- **SHOULD** TSH upper limit of normal be lowered??

JCEM 87:489, 1994

## SUBCLINICAL HYPOTHYROIDISM— HOW COMMON?

- England: 7.5% women, 2.5% men across all age groups TSH >6.0
- Colorado: Median age 56- 9.5% TSH > 5.1 (those taking thyroid Rx-17.5%)
- Older women have higher prevalence
  - 24% women in senior citizen centers
  - Framingham-13.5% women > age 60

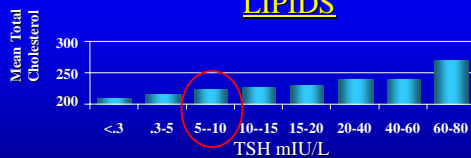
Clin Endo 7:481, 1977 Arch Int Med 160:526, 2000 JAMA 242:247, 1979 Arch Int Med 145:1386 1985

## SUBCLINICAL HYPOTHYROIDISM— HOW COMMON?

### EASIER NUMBERS TO REMEMBER

- Overall prevalence—up to 10% population
- Up to 20% or more in women > 60

## SUBCLINICAL HYPOTHYROIDISM— CLINICAL SIGNIFANCE? LIPIDS



- Compared to euthyroid individuals:
  - Mean LDL 4% higher
  - Mean HDL equal
  - Mean triglycerides 6% higher

## SUBCLINICAL HYPOTHYROIDISM— CLINICAL SIGNIFANCE? CARDIOVASCULAR DISEASE

### Meta-Analysis

- 14 observational studies pooled:
  - CHD risk increased 1.65 fold
  - Risk increased 2.38 fold after pooling for adjusted CV risk factors
  - Both statistically significant
- Conclusions:
  - Subclinical hypothyroidism is associated with CHD
  - ??? whether Rx will affect this not addressed

AJM 119:541, 2006

## SUBCLINICAL HYPOTHYROIDISM— CLINICAL SIGNIFANCE? ALL CAUSE MORTALITY AND CIRCULATORY MORTALITY

### Meta-Analysis

- 11 studies examined relationship mortality and hypothyroidism:
  - Highly discrepant results
  - No clear association
  - ?? perhaps better f/u once hypothyroidism is found explains why less mortality
  - Again no indication as to effect of Rx

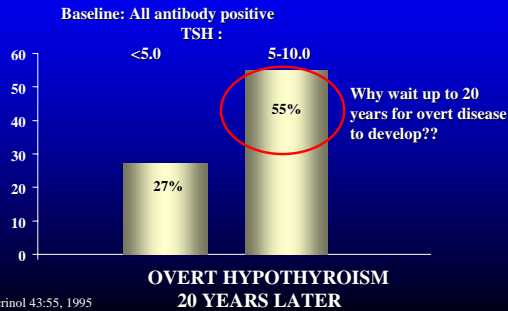
JCEM 92:2421, 2007

## SUBCLINICAL HYPOTHYROIDISM— CLINICAL SIGNIFANCE? MOOD, COGNITION, HEALTH STATUS

- Double blind, crossover study in pts. on T4—euthyroid arm vs subclinical hypoT4 arm over 12 wks.
- Assessments of mood states, health status and memory (working and declarative)
- Euthyroid vs subclinical hypothyroid:
  - Mild decrements in health status and mood-NS
  - Significant decrements in working memory

JCEM 92:2545, 2007

**SUBCLINICAL HYPOTHYROIDISM—  
CLINICAL SIGNIFANCE?  
PROGRESSION TO OVERT HYPOTHYROIDISM**



**SUBCLINICAL  
HYPOTHYROIDISM-Rx OR NOT?  
'EXPERT OPINION'**

'Blue Ribbon' Panel-2004

- Data associating subclinical disease with adverse symptoms/outcomes are few and inconsistent
- Benefits of Rx not clearly documented, consequences of subclinical disease unknown
- **RECOMMENDATION:** Do not Rx
- **EXCEPTIONS:** Pregnancy, women > 60, those at risk for thyroid dysfunction (eg. antibody positivity, goiter)

JAMA 291:229, 2004

**SUBCLINICAL HYPOTHYROIDISM-  
Rx OR NOT?  
'EXPERT OPINION'**

**CONSENSUS STATEMENT: ENDOCRINE SOCIETY  
AAACE, AMERICAN THYROID ASSOCIATION**

- Subclinical hypothyroidism is a continuum of disease.
- Rx most patients with TSH 5-10 mIU/L-key determinant to be the clinical judgment of the provider.
- Rx all patients with TSH >10 mIU/L.
- **DO NOT OVER TREAT !**

JCEM 9:-581, 2004

**SUBCLINICAL  
HYPOTHYROIDISM  
MY CLINICAL JUDGMENT  
WHEN TO Rx**

- When lipids are elevated
- If depression is present
- Antibodies are positive
- Presence of a goiter
- If f/u will be a problem

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## SUBCLINICAL HYPERTHYROIDISM

- Asymptomatic
- Normal T4, FT4
- **Suppressed TSH level**
  - <0.1 diagnostic
  - 0.1-0.3 'gray zone'

## SUBCLINICAL HYPERTHYROIDISM ENSURE THE DIAGNOSIS!

### Low TSH: Differential Dx:

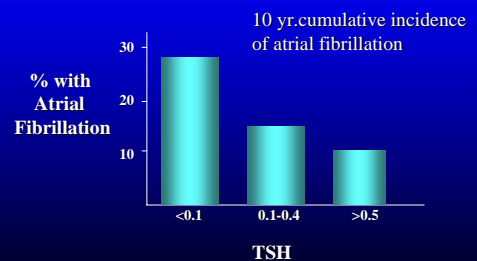
- Severely ill (hospitalized) patients-'sick euthyroid' syndrome.
- Pituitary disease
- T4/T3 Rx
- Amiodarone, Dopamine, Dobutamine Rx
- Recovery from hyperthyroidism

## SUBCLINICAL HYPERTHYROIDISM HOW COMMON?

- Colorado Thyroid Disease Prevalence Study:
  - 25,862 people over 110 sites
  - 2.1 % of patients (median age 56)
  - 20.7% of patients taking T4 Rx

Arch Int Med 160:526, 2000

## SUBCLINICAL HYPERTHYROIDISM CARDIAC PROBLEMS



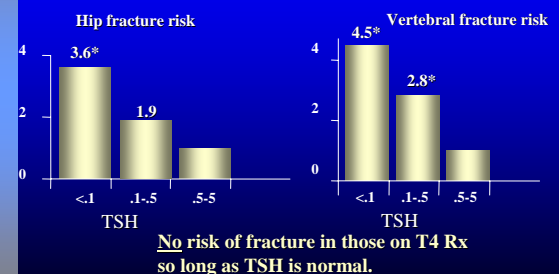
NEJM 331:1249, 1994

## SUBCLINICAL HYPERTHYROIDISM CARDIAC PROBLEMS

- 20% of elderly patients with a. fib. Have subclinical hyperthyroidism
  - 60% will convert with Rx
  - 10% will have an embolic event
- Increased heart rate, PACs, increased LV mass index, decreased LV filling all associated\*

\*JCEM 85:4701, 2000

## SUBCLINICAL HYPERTHYROIDISM BONE PROBLEMS



Ann Intern Med 134:561, 2001

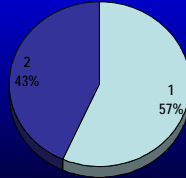
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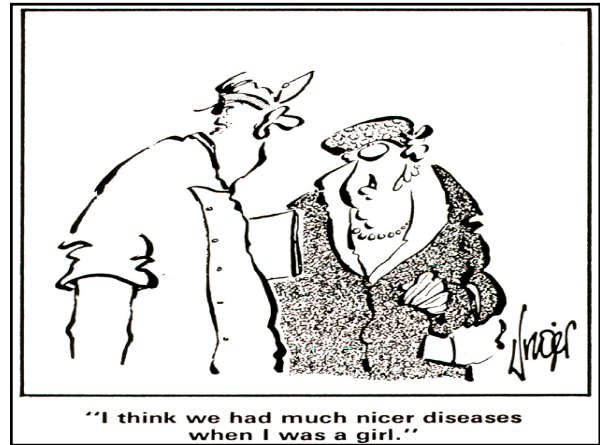
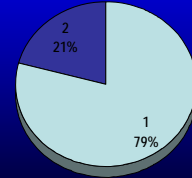
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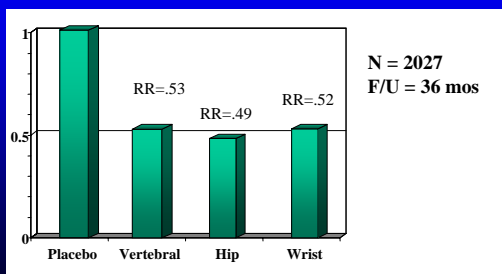
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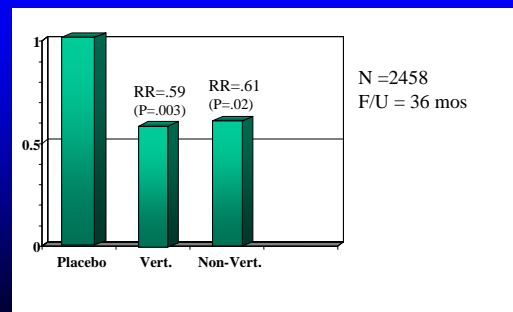
## Effect of Alendronate on Fracture

### (FIT)



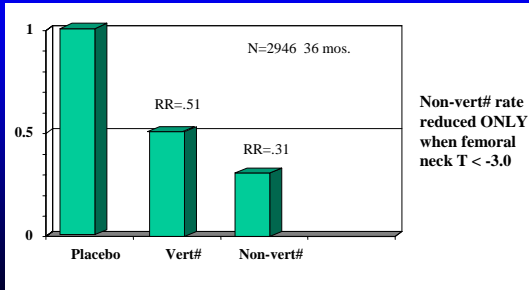
Lancet 1997;349:505

## Effect of Risedronate on Fracture



JAMA 1999;282:1344

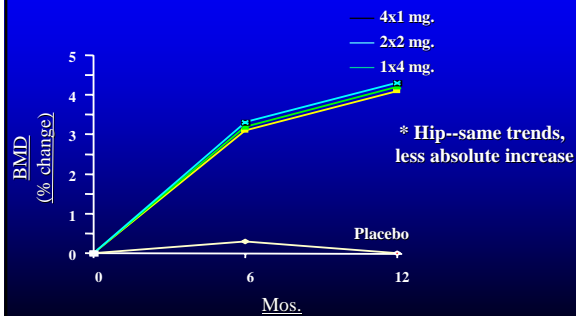
## Effect of Ibandronate on Fracture



JBM 19:1241, 2004

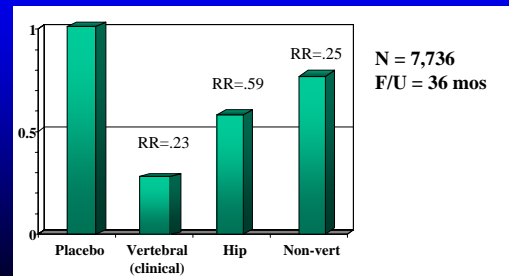


## IV ZOLEDRONIC ACID AND BONE MINERAL DENSITY



NEJM 346:653, 2002

## Effect of Zoledronate on Fracture (5 mg. IV yearly)



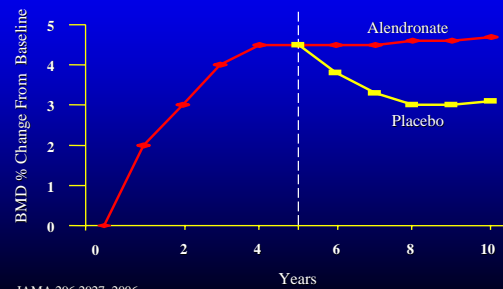
NEJM 356:1809, 2007

## BMD EFFECTS ON DISCONTINUATION OF ALENDRONATE

- FIT/FLEX trial
  - 1099 women randomized to ALN in FIT (5 yrs)
  - Rerandomized to FLEX—5 yrs
    - Continue ALN
    - Placebo
- Endpoints: BMD, biochemical markers, fracture rate

JAMA 296:2927, 2006

## FEMORAL NECK BMD AFTER DISCONTINUATION OF ALENDRONATE



JAMA 296:2927, 2006

## OSTEOMALACIA

### ABNORMAL VITAMIN D METABOLISM

- **Abnormal Absorption/Production**
  - ④ Dietary insufficiency
  - ④ Intestinal malabsorption
    - ④ Sprue\*\*
    - ④ Whipple's
    - ④ Short gut (surgical)
    - ④ Pancreatic insufficiency
  - ④ Hepatic insufficiency
- **Abnormal Metabolism**
  - ④ Vitamin D resistant rickets (1 alpha hydroxylase defic.)
- **Drug Induced**
  - ④ Phenytoin, phenobarbital

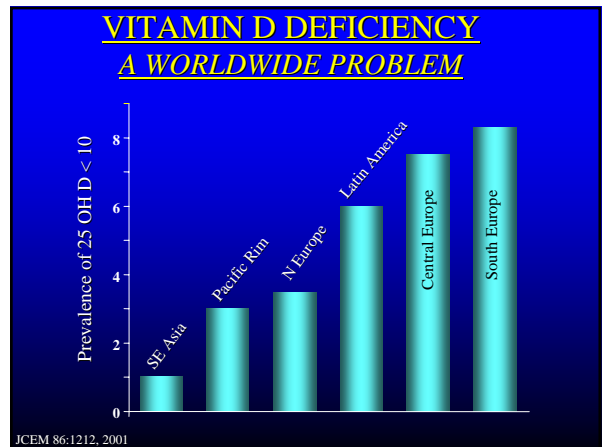
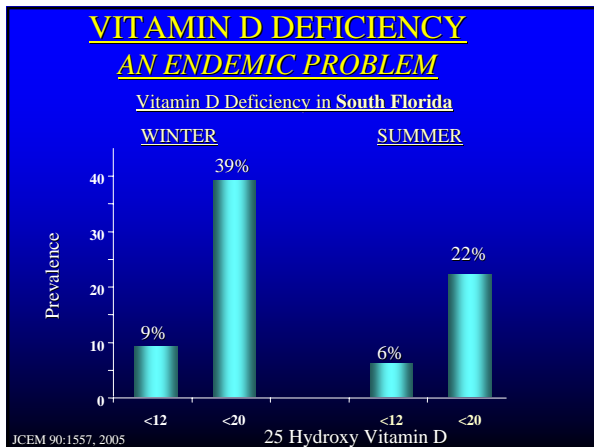
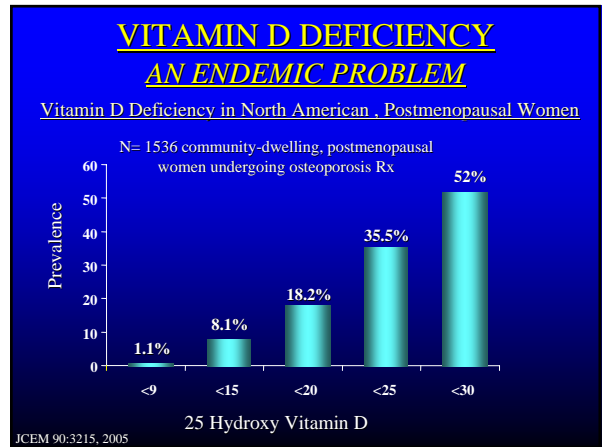
## VITAMIN D DEFICIENCY

### 'PEARLS'

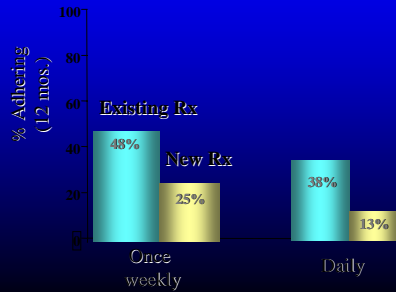
- When assessing, use total 25 hydroxy vitamin D (D2 + D3)
- 3% of human genes affected by vitamin D- relative importance??
- Vitamin D deficiency most common 'disease' worldwide

## CONSEQUENCES OF VITAMIN D DEFICIENCY

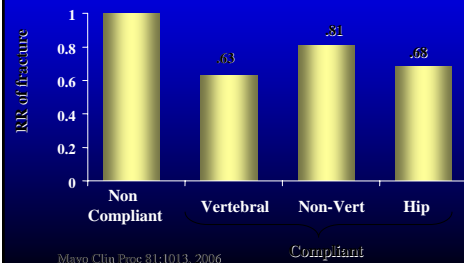
- Ca<sup>++</sup> malabsorption in the gut → reduction in Ca<sup>++</sup> level
- Stimulation of PTH secretion (Vit. D <25-30) → secondary hyperparathyroidism → PO<sub>4</sub> loss
- Increased bone turnover (↓ bone alk phos)
- Osteoporosis—increased fracture risk
- Impaired mineralization--**osteomalacia**



## BISPHOSPHONATE USE ADHERANCE-12 MOS.



## RELATIVE RISK OF FRACTURE AT 24 MOS. Rx COMPLIANCE vs NON COMPLIANCE

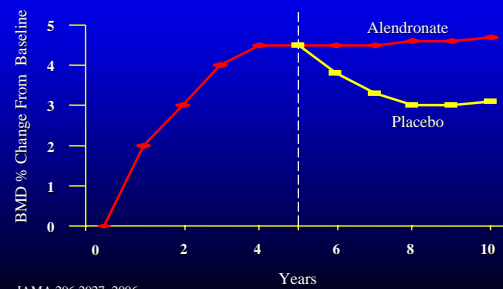


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JAMA 296:2927, 2006