BREAKING NEWS!

Osteoporosis: Review and Update

LEARNING OBJECTIVES

- Why is it important?
- Who should we screen?
- Available methods of screening
- Treatment recommendations
- Monitoring response to treatment

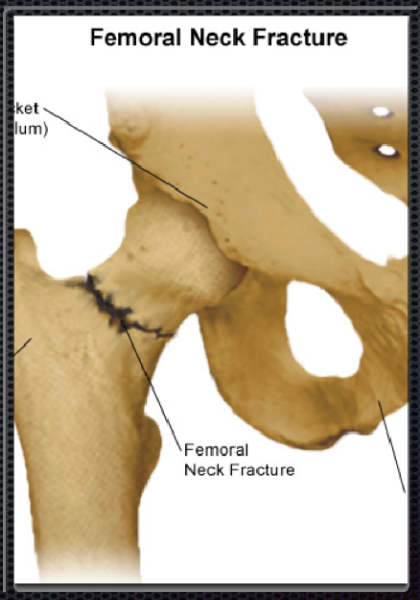
QUESTION!

- The lifetime risk of breast cancer is higher than the lifetime risk for osteoporotic fracture.
  - True
  - False

WHY?

IS IT IMPORTANT

9,000,000 osteoporotic fractures per year



- After age 65:
  - # of hip fractures in women > # of strokes
  - Lifetime risk for hip fracture in women > breast + endometrial + ovarian cancer
  - Lifetime risk for hip fracture in men > clinically significant prostate cancer
  - *approximately 50% of hip fractures that occur after age 80 are in men

MORTALITY

- Hip fractures - associated with a 20% increased mortality within the first year (rate similar to that of patients first year after MI)

Undertreatment of Osteoporosis

- ONLY 22% of high - risk patients > 66 years of age who had recent fracture received BMD testing or were prescribed pharmacologic treatment for osteoporosis
- ONLY 33% with hip fracture were offered treatment

QUESTION!

- The USPSTF recommends screening for osteoporosis for:
  - A. All patients 65 years of age and older
  - B. All women 65 years of age and older
  - C. All women at time of menopause
  - D. Insufficient evidence to recommend screening

WHO?

SHOULD WE SCREEN

USPSTF

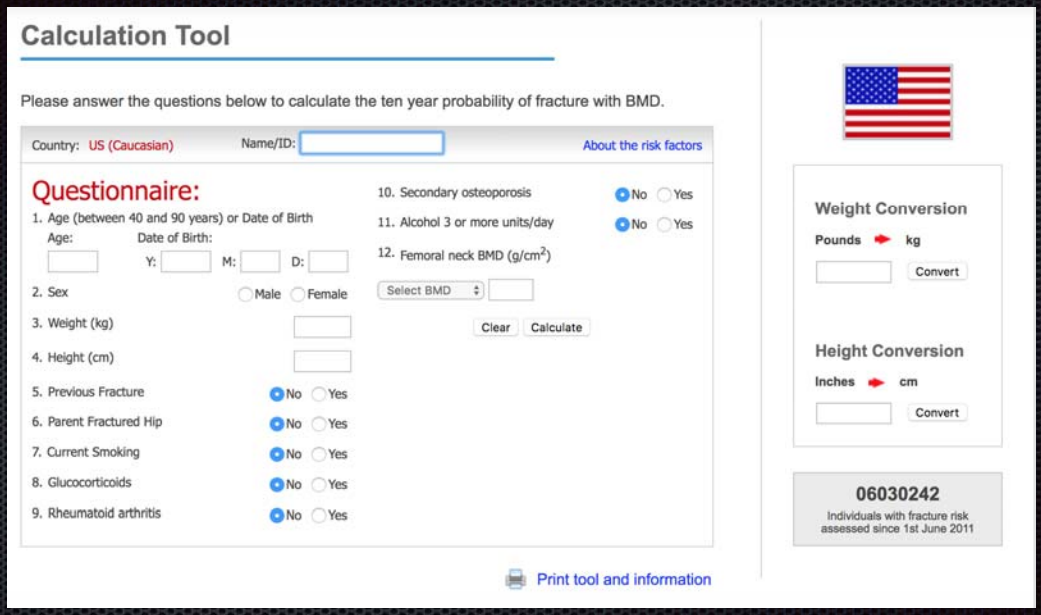
- All women 65 years and older
- Women younger than 65 whose 10 year fracture risk is greater than or equal to that of a 65 year old white woman without additional risk factors
- Insufficient evidence to recommend routine screening for osteoporosis in men

NATIONAL OSTEOPOROSIS FDTN

- Women age 65 years and older and men 70 years and older, regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men age 50-69 with clinical risk factors for fracture
- Adults who have a fracture after age 50 years of age
- Adults with a condition or taking medication associated with low bone mass or bone loss

- Secondary osteoporosis
  - premature menopause
  - hypogonadism (males)
  - malabsorption
  - chronic liver disease
  - IBD
  - hyperparathyroidism
  - Rheumatoid Arthritis

- Additional Risk Factors
  - White or Asian race
  - Immobilization or inadequate activity
  - *Fragility Fracture - “fracture that occurs from a fall standing height or less with no trauma”

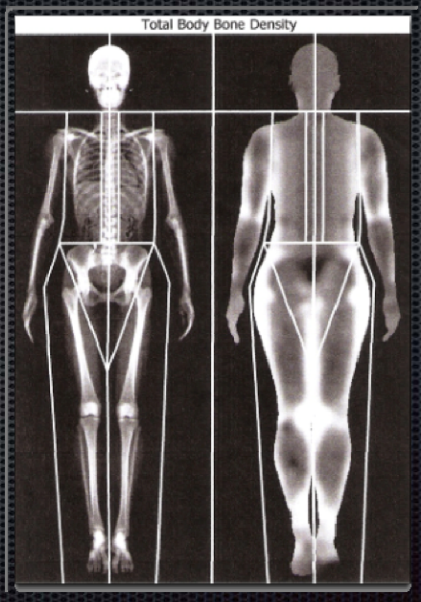


QUESTION!

- The “gold standard” test for osteoporosis is:
  - A. peripheral DEXA
  - B. central DEXA
  - C. ultrasound of heel
  - D. Quantitative CT

BEYOND RISK ASSESSMENT

Testing options



Bone Mineral Density

- Proxy for measuring bone strength (fluoride markedly increased bone density - but bones are brittle)
- Methods for measuring (no longer recommended)
  - peripheral DEXA
  - ultrasound of heel
  - Quantitative CT

- DEXA - Gold Standard
  - Hip and spine measurements most valuable
    - Early menopause associated with greater BMD loss at the spine instead of hip
- WHO defines osteoporosis as -2.5 SD or more greater than the mean peak BMD of young healthy adults (T score)
- Diagnostic threshold - not a treatment threshold

- Biochemical markers
  - Not helpful yet
  - Might be influential in determining response to therapy

- Rescreening
  - “although guidelines for rescreening women with normal initial screening results are lacking, recent evidence suggests that intervals of at least four years appear safe”

DIAGNOSIS

- Normal = T score -1.0 or less
- Low bone mass = T score less than -1.0 and greater than -2.5
- Osteoporosis = T score -2.5 or less
- Osteoporosis = T score -1.1 to -2.4 with fragility fracture
- Severe = T score - 2.5 or less with fragility fracture

TREATMENT

WHO AND HOW

WHO?

- Post menopausal women with T-score less than or equal to - 2.5
- Post menopausal women and men 50 or older with hx of vertebral or hip fracture
- Post menopausal women with osteopenia with 10 year probability of hip fracture of 3% or greater or major osteoporotic fracture combined of 20% or greater (FRAX tool)
- Fragility fracture is an indication for treatment

HOW?

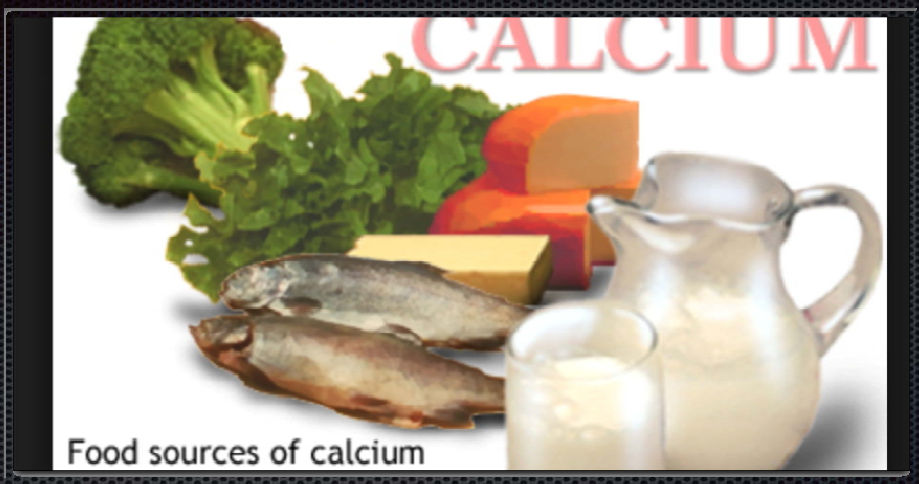
NON PHARM TREATMENT

Fall Prevention

*Muscle strengthening and balance training exercise
*Home environment (25 Tips to Make Home Safe)

EXERCISE

Increase level of physical activity



Calcium and Vitamin D

700-1200mg of calcium from food sources

DIET

Limit intake of alcohol and caffeine

QUIT

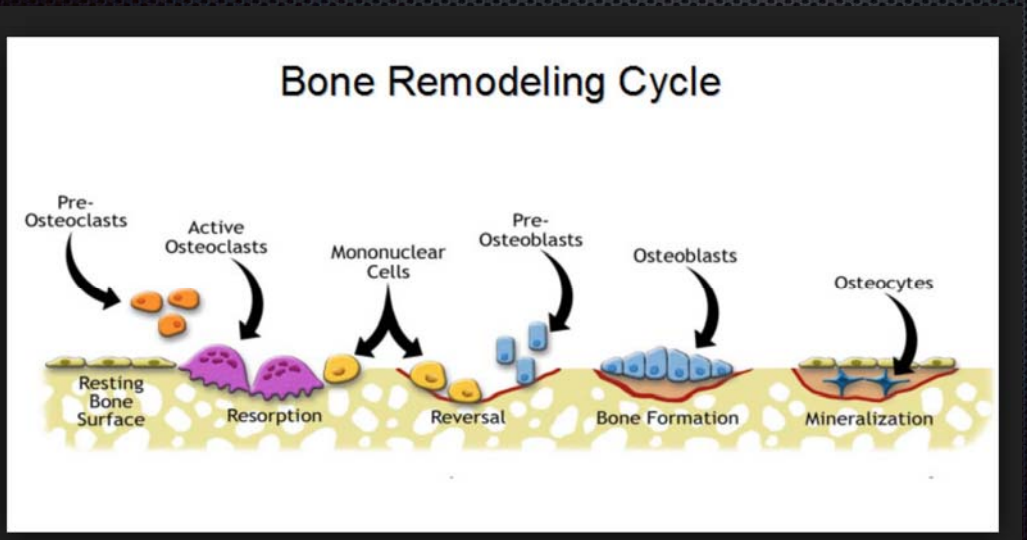
Smoking

HIP PROTECTOR

Questionable benefit

Physiology of Bone

Osteoblast vs Osteoclast



Remodeling - regenerates the skeleton every 10 years

QUESTION!

- The first-line treatment for osteoporosis is:
  - a. calcium 1200mg and vitamin D 800 IU daily
  - b. bisphosphonates
  - c. denosumab
  - d. teriparatide

ANTI-RESORPTIVE THERAPY

- Bisphosphonates:
  - inhibit osteoclast function
  - long-term retention of bisphosphonate in the skeleton (binds to hydroxyapatite in bone)
  - during remodeling, some bound bisphosphonate is released from the bone (metabolically active)
  - those with the highest fracture risk derive the greatest benefit

Antifracture Benefits of Bisphosphonates

Medication (Clinical Trial)	Y	Absolute Fracture Risk Reduction			Relative Fracture Risk Reduction			Number Needed to Treat to Prevent One Fracture		
		Vert fx	Non-vert fx	Hip fx	Vert fx	Non-vert fx	Hip fx	Vert fx	Non-vert fx	Hip fx
Alendronate (FIT I) [4]	3	7.1%	2.8%	1.1%	47.1%	18.9%	50.8%	14	36	90
Alendronate (FIT II) [5]	3	1.7%	1.5%	0.2%	44.3%	11.1%	20.7%	60	68	447
Risedronate (VERT NA) [6] †	3	5.0%	3.2%	0.4%	30.7%	38.1%	19.7%	20	31	276
Risedronate (VERT MN) [7] †	3	10.9%	5.1%	0.5%	37.6%	31.9%	18.2%	9	20	203
Risedronate (HIP) [8]	3	NA	1.8%	1.1%	NA	16.1%	28.2%	NA	56	91
Zoledronic acid (HORIZON PFT) [9]	3	7.6%	2.7%	1.1%	70.0%	25.2%	44.0%	13	37	91
Zoledronic acid (HORIZON RFT) [10]	3	NA	3.1%	1.5%	NA	29.0%	42.9%	NA	32	67
Ibandronate (BONE) [15] †	3	4.9%	−0.9%	NA	62%	−11%	NA	20	NA	NA
Alendronate (Men) [17]	2	5.0%	NA	NA	62%	NA	NA	9	NA	NA
Risedronate (GIO) [18]	1	11.0%	NA	NA	70%	NA	NA	9	NA	NA

Pharmacologic Therapy

- 1st Line - Bisphosphonates
  - Alendronate (available generic) $8 per month (vertebral non vertebral, and hip fractures in women, and vertebral fractures in men, and steroid induced osteoporosis)
  - Risedronate - $87 (same data as alendronate)
  - Ibandronate - no data that it reduces hip fractures - $33

- Zoledronic acid - one vial $260
  - demonstrated to reduce hip and vertebral fractures
  - good alternative for those that cannot tolerate oral bisphosphonates
  - IV once per year, infused over at least 15 minutes
  - IV ibandronate - not proven yet
  - Isolated reports of renal impairment and ARF

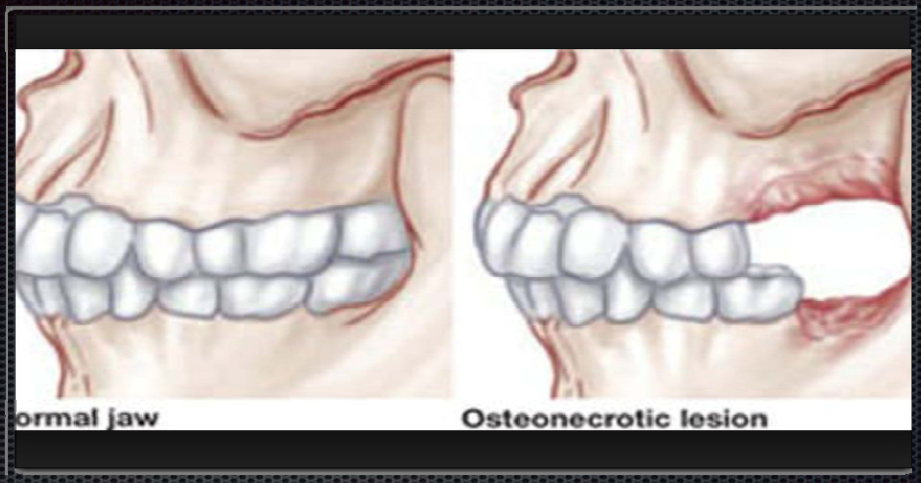
ADDITIONAL BENEFITS

- Decrease in morbidity
- Reduced health care costs
- Significant increase in survival

Precautions

- Check Calcium (bisphosphonates lower calcium) and Vitamin D levels (oral & IV) - correct before IV administration. Goal for Vit D is 25 (correct anything 20 or below)
- Esophageal issues (oral only) - Barrett's, stricture, achalasia, bariatric surgery
- Must be able to be in upright position (oral only)
- Dental work (both oral and IV have increased risk of Avascular necrosis of jaw)
- Flu like symptoms with IV

- Myalgias
- Ocular symptoms
- Cr Clearance must be greater than 35
- Atrial fib*
- Atypical femur fracture *
- Osteonecrosis of the Jaw*
- Esophageal Cancer*



BA-ONJ

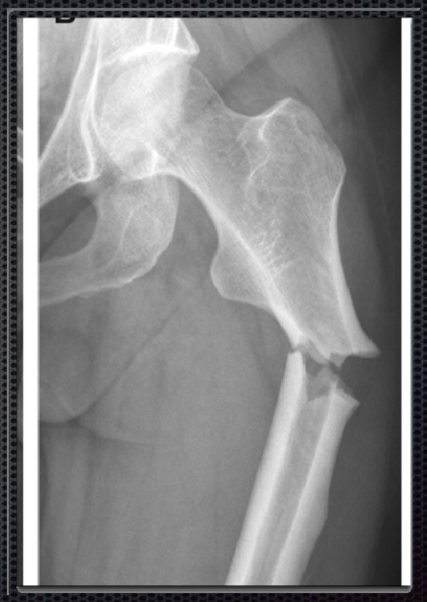
"exposed bone in the maxillofacial region, with no healing within 8 weeks in a patient with bisphosphonate exposure and no hx of craniofacial radiation therapy"

- 95% of cases occur:
  - after invasive dental procedures
  - during oncology therapy
  - with high doses of IV bisphosphonates delivered frequently
  - to an immunosuppressed population

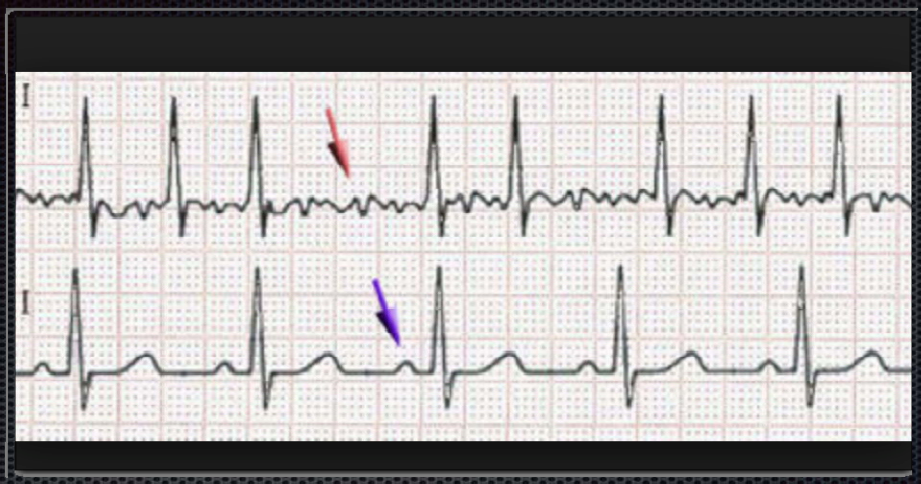
- For oral bisphosphonate therapy
  - incidence unknown
  - estimated risk 1 in 1000 and 1 in 263,000 patient years
  - not related to duration of therapy
  - risk factors may include: poor oral hygiene, glucocorticoid therapy, and chemotherapy
  - ADA

ATYPICAL FEMUR FRACTURES

and bisphosphonates



- estimates of risk are inconsistent
- risk increases with increased duration of bisphosphonate exposure (1.78 AFF per 100,000 patient years when treated for 2 years vs 113.1 AFF per 100,000 patient years when treated for 8-10 years)
- risk rapidly decreases after discontinuing treatment
- “for every subtrochanteric fracture associated with bisphosphonate use, 100 hip fractures were prevented, in addition to prevention of other fractures”

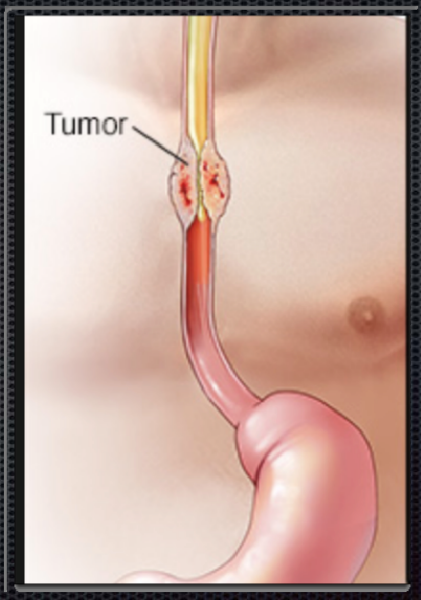


ATRIAL FIB

seen in only one trial with IV Zoledronic acid (1.3% in the treated group and 0.5% in the placebo group)

CANCER OF THE ESOPHAGUS

Controversial - only in one large case controlled study; not reproduced in other studies



- Use immediately after fracture?
  - “To date, there is no clinical evidence that bisphosphonate therapy impairs fracture healing”
  - recommended to wait 4-6 weeks

DURATION OF THERAPY

Is “drug holiday” necessary for bisphosphonates?

a. true
b. false

EXTENSION STUDIES

- FLEX
- VERT-MN
- HORIZON - PFT
- (Note: initially these studies were powered for BMD, but FDA went back to look at fracture data on these extension studies)

FLEX

- Alendronate 70 mg weekly
- 1099 patients
- 10 years (5 years/5 years)
  - alendronate/alendronate (17.7%)
  - alendronate/placebo (16.9%)

VERT - MN

- 164 patients
- max enrollment 7 years
- 0-3 years: placebo/risedronate (32.1% / 20.5%)
- 4-5 years: placebo/risedronate/risedronate (32.1% /19.3%)
- 6-7 years: risedronate for the full 7 years - 13.3%

HORIZON - PFT

- 1233 patients
- Year 0-3: Placebo or zoledronic acid (20% / 9.8%)
- Year 4-6: Zoledronic acid/Zoledronic acid vs Zoledronic acid/placebo (8.6% / 12.0%)

HIGH RISK PATIENT

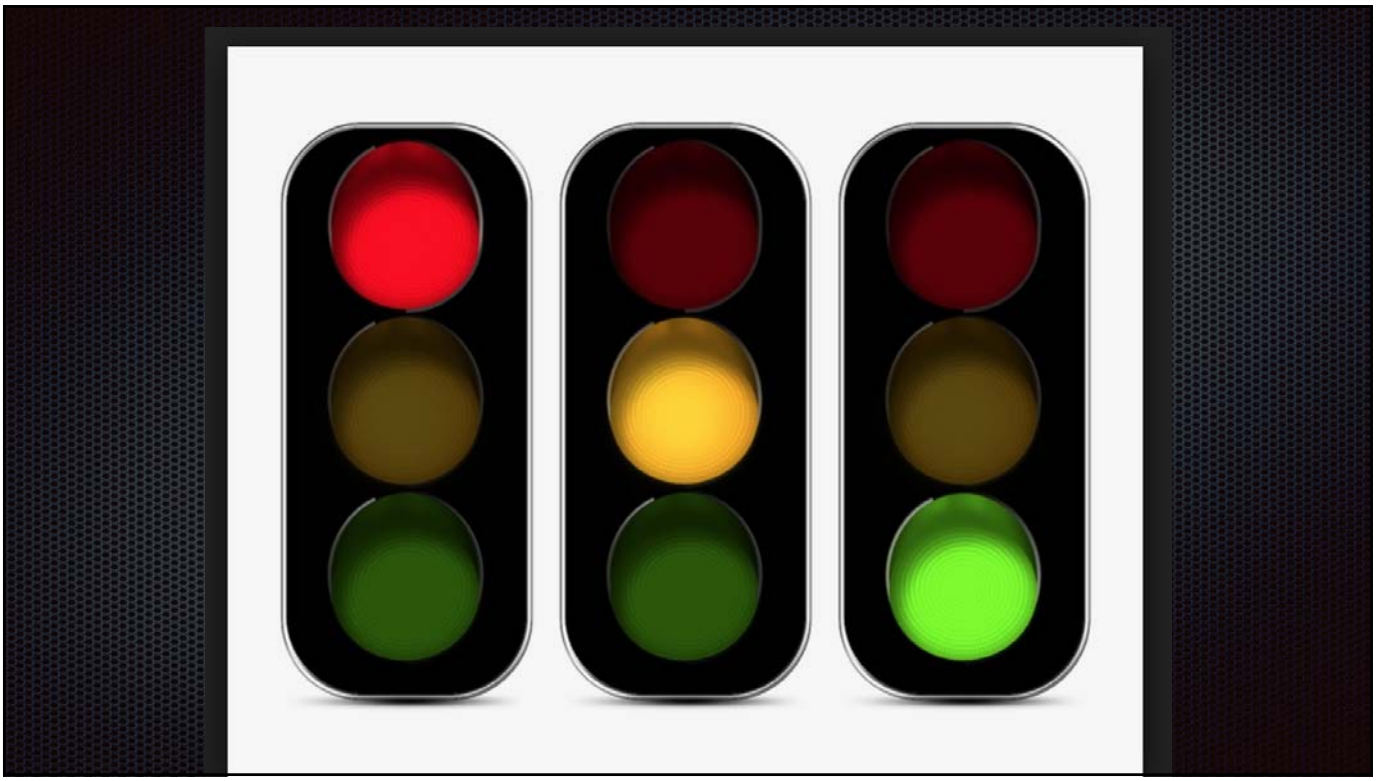
- T score still - 2.5 at the hip
- previous fracture of the hip or spine
- ongoing high-dose glucocorticoid therapy
- ***DRUG HOLIDAY NOT JUSTIFIED
- Re-assess the need for therapy at regular intervals

MODERATE RISK PATIENT

- Hip bone density is better than -2.5 (T score), and no prior hip or spine fracture
- ***Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy.
- Shared decision making!

LOW RISK PATIENT

- Did not meet current treatment criteria at the time of treatment initiation



DENOSUMAB

Anti-resorptive

- Denosumab (Prolia) - $927 per dose
  - RANKL (receptor activator of nuclear factor kappaB ligand)- humanized monoclonal antibody against RANKL; reduces osteoclastogenesis
  - intolerant or unresponsive to bisphosphonates
  - older patients at very high risk
  - patients with impaired renal function
  - given every 6 months subQ
  - decreases vertebral, hip and non vertebral fractures (FREEDOM trial)

Adverse Effects

- Musculoskeletal pain
- Hypercholesterolemia
- Cystitis
- Eczema
- Cellulitis

Precautions

- Correct hypocalcemia and Vitamin D levels
- ONJ and atypical fractures have been reported
- Effects on the immune system (due to inhibition of RANKL)
- Not used for prevention (although studies underway)
- Few studies on men (only those on androgen deprivation therapy)

Duration of Therapy

Few data on ideal duration…efficacy demonstrated up to 10 years

- Variable recommendations on follow up DEXA - every 2 years
- Fracture risk after discontinuation of denosumab - “rebound fracture risk” noted after discontinuation of denosumab 8 to 16 months after the last dose
- Alendronate and Zoledronic acid - have been shown to maintain bone density after discontinuation of denosumab

ANABOLIC AGENTS

Teriparatide and Abaloparatide

- Parathyroid Analog (Teriparatide - recombinant N-terminal human PTH; Abaloparatide - synthetic analog of PTHrP)
- stimulates renal tubular calcium and phosphate reabsorption
- stimulates bone formation and activates bone remodeling
- regulates intestinal calcium absorption

- Pretreatment evaluation:
  - DEXA within 2 years
  - Serum calcium, phosphorus, creatinine, alkaline phosphatase, albumin, 25 hydroxyvitamin D
  - 24 urine calcium, creatinine (or fasting specimen for calcium/creatine ratio) to evaluate for baseline hypercalciuria
  - monitor BP with first dose (increased risk for orthostatic hypotension)

- Teraparatide (PTH) - $2,000/month
  - 20mcg subQ daily for up to 2 years
  - reduces risk of vertebral and non vertebral fractures
  - Expensive
  - Long term safety concerns
  - Investigational dosing (intermittent, and once weekly)

- Abaloparatide
  - 80 mcg subQ daily (prefilled pen with 30 doses)
  - $1800/month
  - 1st dose hypotension

- Adverse events:
  - hypercalcemia
  - hypercalciuria
  - orthostatic hypotension
  - muscle cramps
  - ? osteosarcoma risk

- CONTRAINDICATIONS
  - Primary or Secondary hyperparathyroidism
  - Hypercalcemic disorders
  - Increased baseline risk for osteosarcoma (Paget disease, unexplained A phos, bone mets or skeletal malignancies, hx of prior radiation therapy involving the skeleton)

- After teriparatide….
  - prescribe an antiresorptive (to maintain gains)
  - no “rebound”
  - reduction in fracture appeared to be maintained for at least 18 months after stopping teriparatide

DURATION OF THERAPY

Two years

:D

HORMONE THERAPY & OTHERS

- Raloxifene - $86/month
  - anti-resorptive effects less than bisphosphonates*
  - prevention of osteoporosis (grade 2B)
  - women with increased risk for invasive breast cancer
  - increased risk for thrombotic events, hot flashes
  - no increased risk for heart disease or uterine CA
  - only decreases risk for vertebral fractures
  - do not use in pre menopausal women

- Adverse Effects
  - hot flushes
  - leg cramps
  - peripheral edema
  - increased risk for VTE
  - increased risk for fatal stroke (RUTH trial)

- Estrogen/progesterone therapy
  - no longer first line treatment
  - increased risk for VTE, breast cancer, stroke, and perhaps CAD
  - reduces hip and vertebral fractures

- Calcitonin - $50
  - weak anti-fracture data, vertebral compression fractures only
  - concern about increased cancer risk
  - has a beneficial short-term effect on acute pain relief in patients who have sustained a vertebral fracture

Other therapies

- Calcitriol (steroid induced and post transplant)
- Vitamin K - Japan
- Folate/B12 - higher homocysteine levels
- Androgens
- Isoflavones (genistein and daidzein)

Emerging Therapies

- Sclerostin inhibitors -
- Integrin antagonists -
- Cathepsin K inhibitors -

MONITORING RESPONSE

Is it working?

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