Brittle bones: Pitfalls in the evaluation and management of osteoporosis

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Nothing to disclose

Outline

- Definition
- Epidemiology
- Diagnosis/Diagnostic pitfalls
- Differential diagnosis
- Treatment
- Follow up

Osteoporosis is Common

- Most common bone disease
  - 10 million Americans have osteoporosis and 33.6 million have low bone density at the hip.
  - Over 200 million worldwide
- Approximately 50% of Caucasian women and 20% of men will experience an osteoporotic fracture

Osteoporosis – Definition – DXA*

T ≥ -1, < +2.5 → normal range
T ≤ -1 and ≥ -2.5 → osteopenia
T ≤ -2.5 → osteoporosis
T ≤ -2.5 + fracture → severe osteoporosis

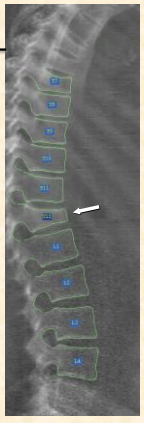
*World Health Organization. WHO Technical Report Series 843. Geneva, 1994.

Two additions to the diagnosis of osteoporosis

- Vertebral fracture analysis – VFA
- WHO FRAX tool

DXA Vertebral Fracture Analysis

- VFA is (new) DXA software
- Detects vertebral fractures
- Based on vertebral shape criteria
- For any given BMD, a fracture on VFA = 5 fold increase in risk of another vertebral fracture, and 2 fold increase risk of non-vertebral fracture

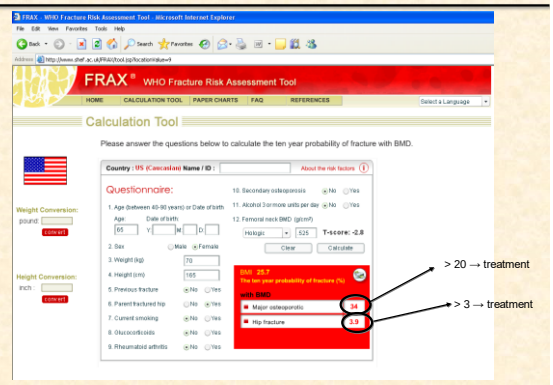


Lewiecki and Laster, JCEM, 2006

FRAX

- Evidence-based tool developed by the WHO
- DXA + Epidemiologic data to assess fracture risk
- http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9 (Google FRAX)

FRAX Tool



Who to Screen with DXA?

Patient Category	Society Recommendations USPSTF	NOF	AACE	ISCD
Women > 65yo	Yes	Yes	Yes	Yes
Women 60-64yo with risk factor	Yes	Yes	Yes	Yes
All women < 65 with risk factors		Yes	Yes	Yes
All women w/fragility fracture		Yes	Yes	Yes
Men aged > 70 years				Yes
All men with a fragility fracture				Yes
Anyone considering therapy for osteop.		Yes		Yes
Women on prolonged HRT		Yes		Yes
Anyone with a disease, condition, or medication associated with osteop.				Yes

USPSTF: US Preventative Services Task Force
NOF: National Osteoporosis Foundation
AACE: Amer. Assoc. of Clinical Endocrinologists
ISCD: International Society of Clinical Densitometry

Other aspects of diagnosis

- other imaging modalities
  - quantitative CT (qCT)
    - very small patients
    - very obese patients
    - precision < DXA
    - poor for monitoring treatment response
- biochemical markers of bone turnover
  - utility in an individual is limited
  - diagnosis – high vs: low turnover
  - treatment - monitor response to a therapy

Biochemical Markers of Bone Turnover

- Resorption
  - N-telopeptide Collagen Crosslinks (NTX)
  - C-telopeptide Collagen Crosslinks (CTX)**
  - Pyridinoline
  - Deoxypyridinoline
- Formation
  - Bone Specific Alkaline Phosphatase
  - Osteocalcin
  - PINP (Procollagen Type I Intact N-Terminal Propeptide) **

** Commonly used

Glucocorticoid-Induced Osteoporosis (GIOP)

- Most common form of secondary osteoporosis
- Bone loss can be rapid (up to 20% in 6 months)
- Fractures common (up to 50% on chronic steroids)
- Fractures occur at higher BMD than typical osteoporosis patients
- Often untreated (only 10% have a DXA, 40% on osteoporosis medication)

ISCD

GIOP Treatment Recommendations

American College of Rheumatology — Education • Treatment • Research

- Prescribe adequate calcium and vitamin D to all

	Daily Dose	Treatment*
Postmenopausal women and men ≥50	≥7.5 mg	Yes
	≤7.5 mg	
	FRAX ≤10%	No
	FRAX >10%	Yes
Premenopausal women and men<50	**Treat only if history of fracture**	
Men and non-childbearing women	≥5 mg	Yes, if fracture
Childbearing women	≥7.5 mg	Yes, if fracture

*FDA approved: alendronate, risedronate, zoledronate, Denosumab and teriparitde

ISCD

Pitfalls of DXA

- DXA-based fracture and drug efficacy predictions are derived from data on postmenopausal women primarily
- In men, premenopausal women and children these DXA diagnostic criteria (osteoporosis, osteopenia) do not apply
- Positioning – small changes in positioning of the patient and the software can lead to significant changes in values
- Patient size – DXA underestimates the BMD of small-boned persons
- Does NOT diagnose osteomalacia

Bone strength

Bone quantity - DXA
+
Bone quality - ???
→ Bone Strength

• The inability to assess bone quality (non-invasively) is the major barrier in the diagnosis and treatment of osteoporosis.

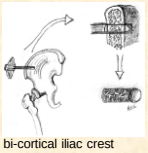
• This has led to an imbalanced reliance on DXA results for the diagnosis of osteoporosis.

How do we assess bone quality?

- **Personal fracture history**
  childhood fractures predict adult fractures
- **Personal medical history**
  h/o of glucocorticoids, anticonvulsants, milk allergy (poor calcium intake), diabetes mellitus, HIV
- **Family history**
  first degree relatives with height loss/pathological fractures/osteoporosis

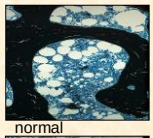
DXA is the single best, widely available predictor of fracture risk available today!

Diagnosis: Bone biopsy with histomorphometry – gold standard

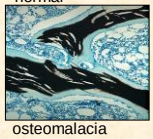


bi-cortical iliac crest biopsy

tetracycline labeling



normal



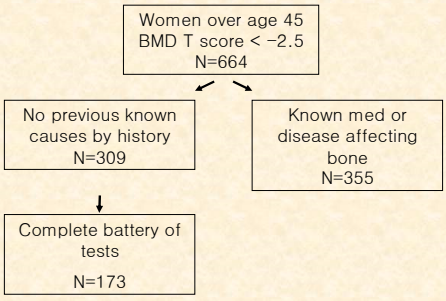
osteomalacia

Can measure:
- # osteoblasts per bone surface
- # osteoclasts per bone surface
- bone formation rate
- mineral apposition rate
- much more

Good for pinpointing the locus of the defect and mixed bone diseases

Laboratory evaluation for causes of secondary osteoporosis

Tannenbaum, JCEM 2002, 644 women at an "osteoporosis" clinic



Cause Identified by Medical History, N = 355

• Oral glucocorticoid treatment	36%
• Premature ovarian failure**	21
• Malnutrition	10
• Alcoholism	10
• Liver disease	10
• Immobilization > 3 months	9
• Systemic chemotherapy	8
• History of hyperthyroidism	6
• Anticonvulsant use	5
• RA or SLE	5
• Hyperparathyroidism	5
• Intestinal Malabsorption	4
• Other known disorder or medication	6

****This study tested only women; up to 30% of men with osteoporosis are hypogonadal**

Disorders Discovered by Testing (n = 173)

• Hypercalciuria	17	10%
• Malabsorption	14	8%
• Hyperparathyroidism	12	7%
– Primary (1)		
– Secondary (poor dietary Ca)(11)		
• Vitamin D deficiency (< 12.5 ng/ml)	7	4%
• Exogenous hyperthyroidism	4	2%
• Cushings disease	1	1%
• Hypocalciuric hypercalcemia	1	1%
At least one new diagnosis	**55**	**32%**

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• Vitamin D deficiency **(< 20 ng/ml)**	36	21%
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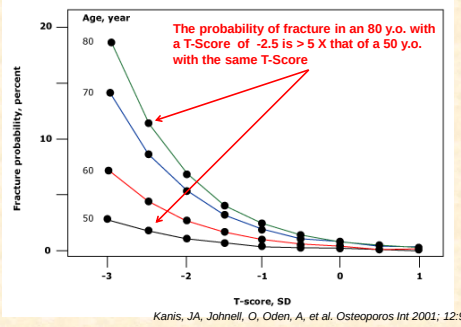
• Hypocalciuric hypercalcemia	1	1%
At least one new diagnosis	**85**	**49%**

Age is an Independent Risk Factor for Fracture



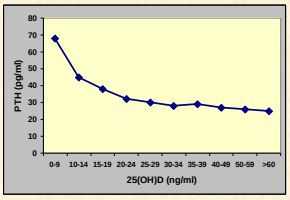
Kanis, JA, Johnell, O, Oden, A, et al. Osteoporos Int 2001; 12:989.

Minimum evaluation for secondary (underlying causes) of osteoporosis

- Gonadal status
- Thyroid function tests
- Calcium, PTH, 25 vitamin D
  - low D - malabsorption
- 24 hour urine calcium (cortisol?)
- Serum phosphorus

Cohen Adi, Shane E. Primer ASBMR 2009;289-293

What is the desirable normal vitamin D concentration, and the appropriate dose for daily consumption?



- PTH values plateau at 32 ng/ml
- supported by multiple studies
- ***32 ng/ml*** = desirable serum 25 OH-D level for bone health

Holick, et al JCEM, 2005

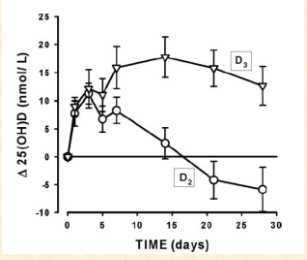
Thomas, et al NEJM 1998

What is the optimal dose and form of vitamin D?

- The RDA (400 IU/day) is too low
- Debate over what is enough/too much
- 1,000 – 2,000 U/day is probably optimal
- In case of severe deficiency, fill the tank with high doses of vitamin D (50, 000 IU once/week for 8 weeks) and then 1000-2000 U/day.

Forms of vitamin D

- D2 – ergocalciferol, plant sterol
- D3 – cholecalciferol, animal-derived



- serum vitamin D levels after oral loading of vitamin D
- D3 is superior to D2

Armas, JCEM 2004

Forms of vitamin D

- No parenteral forms of D2 or D3 in US currently
- UV light for patients with malabsorption
  - dose/time uncertain – due to variability in sunlight/tanning machine intensity
  - empiric – can be as little as 15 min./week
  - check blood levels in response to tanning

Summary: evaluation of patients with osteoporosis

- Many patients with low bone mass have identifiable abnormalities
- Patients with osteoporosis should have a comprehensive evaluation
  - History and Physical Examination
  - Chemistry Panel Including Phosphorus
  - 24 hour urine calcium, 25 OH-D, PTH, SPEP/UPEP testosterone, (24 hr urine cortisol)
- Greater emphasis should be placed on adequate calcium and vitamin D nutrition

Non-Pharmacologic Therapy

- Nutrition
  - Calcium
  - Vitamin D
- Exercise
  - Weight-bearing
- Fracture management
  - Physical Therapy
  - Surgery

Non-Pharmacological Therapy NOF Recommendations

- Adequate intake of dietary calcium and vitamin D
  - Calcium: 1000 -1200 mg/day
  - Vitamin D: 800-1000 IU/day
- Regular weight-bearing and muscle-strengthening exercise
- Avoidance of smoking and excess alcohol
- Fall prevention

National Osteoporosis Foundation Clinicians Guide 2013

Physical Therapy Basics for Osteoporosis

- Discourage
  - Heavy lifting
  - Back flexion
- Encourage
  - Fall prevention
  - Balance exercises
  - Weight bearing exercise eg walking
  - Back extension exercises

Assess Fall Risk

- ASK: Have you fallen in the last year?
- EVALUATE:
  - Muscle strength
    - Sit-to-stand without the use of arms
  - Balance
    - Heel-to-toe walking
    - Stand on one foot (begin with holding your hand or counter)

Prevention of Falls

- Correct visual and hearing impairment
- Optimize medications
- Bathroom grab-bars and nonskid mats
- Avoid throw-rugs and slippery mats
- Keep electric and telephone cords away
- Reduce clutter from walking areas
- Nightlight in bedroom and bathroom
- Handrails on steps and stairs
- Walking aids, if needed
- Exercise for strength and balance (T'ai Chi)

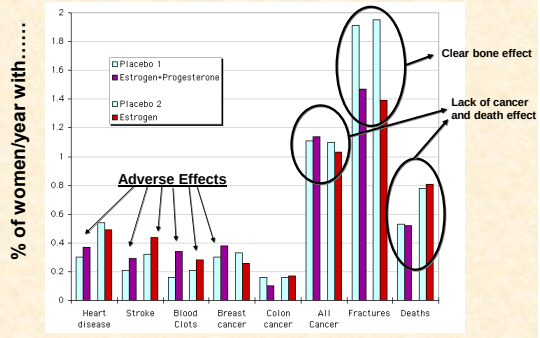
Pharmacologic Therapy

- Antiresorptive
  - Block osteoclastic bone resorption
- Anabolic
  - Promote osteoblastic bone formation

Pharmacologic Therapy

- **Anti-resorptive**
  - Estrogen
  - Calcitonin
  - Raloxifene
  - Bisphosphonates
  - Denosumab

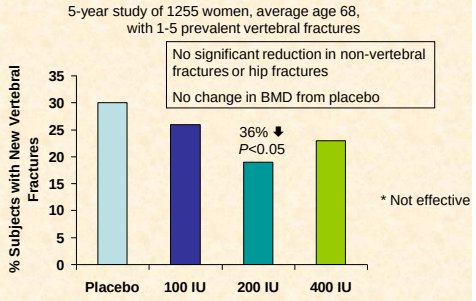
Estrogen - Results from the Women's Health Initiative - Side Effects



While estrogen remains one of the more potent drugs in the prevention and treatment of osteoporosis, its current place in the armamentarium is unclear.

Nasal Calcitonin Reduces Spine Fractures*

PROOF Trial: Prevent Recurrence of Osteoporotic Fractures



Chesnut CH III, et al. *Am J Med*. 2000;109:267

Raloxifene

- SERM (selective estrogen receptor modulator) also known as EAA (estrogen agonist/antagonist)
- BMD: increases at spine and hip
- Fractures: reduces risk of vertebral fractures 30-50%, no proven benefit for hip or non-vertebral fractures
- Extra-skeletal:
  - reduces risk of breast cancer
  - does not reduce hot flashes
  - AE's: VTE risk, leg cramps

Ettinger B, et al. *JAMA*. 1999;282:637.

Bisphosphonates

- Alendronate: po daily or weekly
- Risedronate: po daily, weekly or monthly
- Ibandronate: po monthly or IV q 3 months
- Zoledronic acid: yearly IV

Bisphosphonate Characteristics

- Poorly absorbed
  - ~ 50% excreted by kidney
  - ~ 50% binds to bone
- High affinity to bone –
  - Binds preferentially at resorptive surfaces
  - Induces osteoclast dysfunction
- Long skeletal half-life

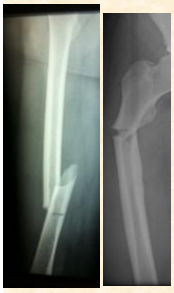
Fracture Risk Reduction with Bisphosphonates in RCTs

- Pivotal fracture trials
  - Alendronate: FIT 1, FIT 2
  - Risedronate: VERT, HIP
  - Ibandronate: BONE
  - Zoledronic acid: HORIZON
- Results
  - Spine fractures reduced ~50% in all
  - Hip fractures reduced ~40% with alendronate, risedronate and zoledronic acid

Bisphosphonate Safety

- Possible GI intolerance with oral agents
- Not recommended for GFR < 30-35 ml/min
- Acute phase reaction with IV
- Hypocalcemia
- Osteonecrosis of the jaw (ONJ)
- Atypical femoral fractures

Atypical Femur Fractures
Major Features



Diaphyseal fracture with 4 of 5 criteria required for diagnosis:

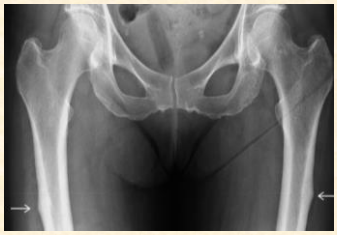
- Associated with minimal or no trauma
- Fracture line originates at the lateral cortex
- Complete fractures extend through both cortices often with medial spike; incomplete fractures involve only the lateral cortex
- Non-comminuted or minimally comminuted
- Localized periosteal or endosteal thickening of the lateral cortex at the fracture site ("beaking" or "flaring")

45

Shane E et al *J Bone Miner Res* 2013;29:1-23

Atypical Femur Fractures
Minor Features

Associated but not required for diagnosis



- Increased cortical thickness of diaphysis
- Unilateral or bilateral prodromal symptoms: dull or aching pain in the groin or thigh
- Bilateral incomplete or complete femoral diaphysis fractures
- Delayed fracture healing

Shane E et al. *J Bone Miner Res* 2013;29:1-23

Important to Balance Risks vs Benefits

- The incidence of AFF increases with longer duration of bisphosphonate use and higher dose.
- The rate is much lower than the expected rate of devastating hip fractures in elderly osteoporotic patients.
- Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates.
- The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years.

Bisphosphonates and Osteonecrosis of the Jaw

- Risk only apparent with very high doses
- 2007 JBMR review
  - Dental exam prior to treatment (high dose)
  - Usual dental care – don't stop drug for care

Bisphosphonates – falsely accused of ONJ

- ONJ risk in 10 years < death from MVA < anaphylaxis from flu shot
- ONJ 1:40,000
- Bisphosphonates decrease # by 40% (statins decrease CV mortality by 40%)
- NNT 1:10 for fractures (NNT 1:56 to prevent CVD by statins)
- Treating 1000 pts with BPs for 3 years prevent 100 fractures
- In AFF, bone turn over markers are not always suppressed

Denosumab

- Anti-resorptive, fully human monoclonal antibody, binds and inhibits RANKL (RANKL triggers activation of osteoclasts)
- BMD: increases at spine and hip
- Fracture: decreases spine, hip and non-vertebral fracture by 68%, 40%, 20%
- Injection SQ every 6 months
- Safety: increased infection risk. Avoid in HIV/IC patients.

Cummings *N Engl J Med* 2009; 361[8]:756-765

Teriparatide: rhPTH(1-34)

- Class: anabolic hormone
- Fractures: decreases spine and non-vertebral fractures by 65% and 53%, no proven benefit for hip in RCT
- Extra-skeletal considerations:
  - Osteosarcoma in rats, daily subcutaneous injection, refrigeration, hypercalcemia, leg cramps, dizziness, high cost, limit of 2 years of therapy

Neer RM, et al. *N Engl J Med*. 2001;344:1434.

Summary: BMD Response

Medication	Spine	Hip
Estrogen	⬆⬆⬆	⬆⬆
Alendronate	⬆⬆⬆	⬆⬆
Risedronate	⬆⬆⬆	⬆⬆
Ibandronate	⬆⬆⬆	⬆⬆
Zoledronic acid	⬆⬆⬆	⬆⬆
Calcitonin	~	~
Raloxifene	⬆⬆	⬆
Denosumab	⬆⬆⬆	⬆⬆
Teriparatide/ Abaloparatide	⬆⬆⬆⬆	⬆

Summary: Fracture Risk Reduction (PMO)

Medication	Spine	Hip	Nonvertebral
Estrogen	✓	✓	✓
Alendronate	✓	✓	✓
Risedronate	✓	✓	✓
Ibandronate	✓		
Zoledronic acid	✓	✓	✓
Calcitonin	✓		
Raloxifene	✓		
Denosumab	✓	✓	✓
Teriparatide/Abl	✓	✓	✓

We now have multiple choices for prevention and treatment of osteoporosis

How do we follow up on the patient?

Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis

– How is treatment monitored?
  - Baseline DXA spine or total hip, repeat every 1-2 years until stable
  - Follow-up scans should be in the same facility, with the same machine, and, if possible, with the same technician

- What is successful treatment?
  - ◊ BMD stable or increasing, no fractures
  - ◊ For anti-resorptive agents, bone turnover markers at or below the median value for premenopausal women
  - ◊ One fracture not necessarily evidence of failure

Watts et al *Endoc Pract* 16(6):1016-9, 2010

What is considered a treatment failure?

- Two or more incident fragility fractures.
- One incident fracture and an elevated baseline serum CTX that does not decrease by 25% while on antiresorptive therapy (or, a serum P1NP that does not increase by 25% while on anabolic therapy).
- One incident fracture and a clinically significant decrease in BMD at the spine (5%), or at the hip (4%).

MTP, Endo Society 2015, 2018

A rational approach to patients who fracture after at least 6–12 months on therapy

- Assess for compliance and absorption
- Assess for secondary causes of osteoporosis
- Assess BTMs and BMD
- If there is evidence of poor compliance, malabsorption, inadequate BTM response, or significant decline in BMD in addition to a single fragility fracture, then therapy should be changed.

Cosman F. Curr Osteoporos Rep. 2014;12:385-395

Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis

- How long should patients be treated?
  - For bisphosphonates, if osteoporosis is mild, consider a "drug holiday" after 4 to 5 years of stability
  - If fracture risk is high, consider a drug holiday of 1 to 2 years after 10 years of treatment
  - Follow BMD and bone turnover markers during a drug holiday period & reinitiate therapy if bone density declines substantially, bone turnover markers increase, or a fracture occurs

Watts et al *Endoc Pract* 16(6):1016-9, 2010

Thank You

For those who are > 30 years, enjoy today as you will have less bone tomorrow!!