Osteoporosis — Concepts, Diagnosis, Treatments

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Content
- Definition and epidemiology
- Primary and secondary risk factors
- Bone pathophysicsology
- Diagnostic approach
- Universal prevention
- Pharmacologic treatment options
- "Bones of glass and a heart of stone"

Definition; NIH Consensus Conference
- "A skeletal disorder characterized by compromised bone strength..."
- "...predisposing to an increased risk of fracture."
- Strength = Density + Quality

Epidemiology of Osteoporosis
- 8 mio. Women, 2 mio. Men have osteoporosis
- 34 mio. have low bone mass
- In the US, 50% of women and 25% of men >50 yo. will suffer an osteoporosis related fracture
  - 300.000 hip
  - 400.000 wrist / forearm
  - 550.000 vertebrae
  - 810.000 other

Economic Burden (per year)
- $25.3 billion by 2025
- $50 billion by 2050
  - $17 billion direct medical costs
  - >400,000 hospital admission
  - ~2.5 mio. physician visits
  - >180,000 nursing home admissions

Risk Factors
Primary Risk Factors
- Caucasian / Asian background
- Women
- Age / Postmenopausal status
- Menopause < age 45
- Small body habitus
- Hx. low trauma fracture in 1st degree relative

Secondary Risk Factors
- GI disorders leading to malabsorption (bariatric surgery, inflammatory dz., celiac dz. etc.)
- Endocrine
  - Hyperparathyroidism (primary or secondary)
  - Hyper/hypothyroidism
  - Hypercortisolism
  - Hyperprolactinemia
  - Acromegaly
  - Hypogonadism

Less Common Secondary Risk Factors
- Ankylosing spondylitis
- COPD
- Endometriosis
- Hemophilia
- Hemochromatosis
- Hypophosphatemia

Primary Risk Factors
- Dementia / impaired vision
- Falls
- Low physical activity
- Alcohol intake
- Smoking
- Low lifelong calcium intake

Secondary Risk Factors
- Liver disease (biliary sclerosis, autoimmune and alcoholic hepatitis, sclerosing cholangitis)
- Rheumatoid arthritis and other autoimmune diseases
- Renal disease
- Transplantation
- IDDM
- Dietary disorders (anorexia etc.)

Less Common Secondary Risk Factors
- Ankylosing spondylitis
- COPD
- Endometriosis
- Hemophilia
- Hemochromatosis
- Hypophosphatemia

Medications
- Glucocorticoids (PO and inhaled)
- GRH Agonists
- Depo-Provera
- Immunosuppressants
- Anticonvulsants
- Cytotoxic drugs
- Lithium
- Long-term heparin / coumadin
- PPI
- SSRI
Remodeling sites in negative balance

Low Turnover State

Slow bone loss

High Turnover State

Rapid bone loss

Bone remodeling abnormalities resulting in bone loss

f = bone formation
r = bone resorption

Pathogenesis of Osteoporotic Fractures

Aging
Menopause
Increased bone loss
Low peak bone mass
Low bone density
Poor bone quality
Propensity to fall
Fractures
WHO Definition

- Distribution of BONE MINERAL DENSITY in young, healthy adults
- T-score = standard deviation (SD) below or above mean of young healthy adults
- Specific to vertebrae, hip, wrist

BMD measurement

- Goal: to diagnose low bone mineral density AND estimate fracture risk
- Population (NOF guidelines):
  - Women >65 yo regardless of risk factors
  - Postmenopausal women with risk factors (except race)
  - Postmenopausal women with fractures

Serial BMD measurements

- Monitor therapy: recommended every 1-2 years
- Change must exceed least significant difference
- Medicare coverage every 2 years:
  - Postmenopausal women
  - Long-term steroid therapy
  - Vertebral abnormalities
  - Primary hyperparathyroidism
  - Monitor response to therapy

Combined Effect of Bone Density and Prevalent Fractures

- Relative Risk for New Vertebral Fractures

Laboratory tests for Osteoporosis Mt. Sinai Study

- Cross-sectional chart review
  - 664 peri- or postmenopausal women (≥ 45 yrs) with BMD T-score < -2.5
  - 309 without known osteoporosis risk factors
  - 173 had complete set of laboratory tests

Mt. Sinai Study: Findings

- 55 / 173 patients with ≥ 1 new diagnosis
- 32.4% of 173 patients =
Suggested Screening Tests for Contributory Causes of Osteoporosis

- 24-hour urine:
  - Ca, creatinine and Na
- Serum:
  - Ca, P, creatinine, alkaline phosphatase, albumin, PTH and 25-OH vitamin D, TSH, SPEP
- Moderate cost, misses only rare causes of secondary osteoporosis
- Turnover marker???

Universal Preventive Measures

Fracture Prevention

- Risk prevention (falls, balance etc.)
- Weight bearing + muscle strength exercises
- Smoking cessation, EtOH avoidance

Exercise guidelines

- Avoid
  - Forward flexion of spine
  - Bending forward from the waist
  - Twisting / jerking of spine
- One foot to remain on the ground

Balance training

- Face countertop and hold on with both hands
- Bend one leg and bring foot behind body
- Count to 5
- Then repeat with
  - One hand holding on
  - Fingertip
  - Without holding on
  - Closed eyes

General fall prevention

- Handrails
- Wear shoes with low heels
- Sufficient lighting, use flash light
- Rubber mat in shower
- Skid-proof carpets / rugs
- Cordless phone
- Emergency service / neighbors
**Calcium – daily intake**

- **1 – 3 years**: 500 mg
- **4 – 8 years**: 800 mg
- **9 – 18 years**: 1300 mg
- **19 – 49 years**: 1000 mg
- **> 50 years**: 1200 mg
- **Pregnancy:**
  - **< 18 years**: 1300 mg
  - **> 19 years**: 1000 mg

**Food Sources**

- **Yoghurt, low fat, 8 oz.**: 250-380 mg
- **Shredded cheddar, 1.5 oz.**: 306 mg
- **Milk 2%, 8 oz.**: 297 mg
- **Soy beverage, 8 oz.**: 80-500 mg
- **Tofu, processed with Ca**: 204 mg
- **Instant breakfast, 8 oz.**: 100-500 mg
- **Orange juice with Ca, 8 oz.**: 260-325 mg
- **Cereal, 1 cup**: 100-1000 mg
- **Ice cream, 1 cup**: 85 mg

**Vitamin D**

- Active vit. D essential for Ca absorption
- Calcitriol (1,25 (OH) ––vit. D)
- Target serum 25-(OH) vit. D > 30 ng/ml
- Daily need:
  - < 50 years: 400-800 IU/d
  - > 50 years: 800-1000 IU/d

**Pharmacologic Treatment**

- Alendronate / Risedronate
- Calcitonin
- Raloxifene
- ET/HT
- Teriparatide

**Therapy Indications**

- Central T score < -2, no risk factors
- Central T score < -1.5, with risk factors
- History of low-trauma vertebral or hip fracture

**Therapeutic Classes**

- Bone retaining (anti-resorptive):
  - Bisphosphonates
  - Calcitonin
  - Estrogen / Hormone therapy
  - Raloxifene
- Bone forming (anabolic):
  - Teriparatide
Bisphosphonates

- FDA approved:
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Binds irreversibly to hydroxyapatite at the osteoclast-bone interface

Alendronate Indications

- Osteoporosis prevention (5 mg QD, 35 mg qweek)
  - Postmenopausal women
- Osteoporosis treatment (10 mg QD, 70 mg qweek)
  - Postmenopausal women
  - Men
  - Steroid-induced in men and women

Early in the morning
- 8 oz. tap water
- NPO for 30 min (Alendronate, Risedronate) or 60 min (Ibandronate)
- Upright for 30 min

Alendronate – GIO 2 years

Risedronate – 1 year

Risedronate Indications

- Osteoporosis prevention (5 mg QD, 35 mg qweek)
  - Postmenopausal women
  - Steroid-induced in men and women
- Osteoporosis treatment (10 mg QD, 70 mg qweek)
  - Postmenopausal women
  - Men
  - Steroid-induced in men and women

Calcitonin

- Reduces vertebral fractures
- Not shown to reduce non-vertebral fractures
- Indication: postmenopausal (>5 years) women who are unable to tolerate other treatments
- Nasal spray or SQ
Calcitonin – 5 years

Cumulative percentage of participants with at least one new fracture per year. Number of participants with follow-up radiographs (placebo = 270, 100 IU = 273, 200 IU = 287, 400 IU = 278). The asterisk indicates \( P < 0.05 \) versus placebo.

Raloxifene

- Selective \( E_2 \) receptor modulator
  - Agonist on bone
  - Antagonist on breast + uterus
- Osteoporosis prevention
  - Postmenopausal women
- Osteoporosis treatment
  - Postmenopausal women

Raloxifene – Breast Cancer

- MORE: 4 years Raloxifene = 72% reduction breast cancer in incidence
- CORE: 8 years Raloxifene = 66% reduction in breast cancer incidence

Women’s Health Initiative

- ET: Conj Estrogen (Premarin®)
- HT: Conj Estrogen + Medroxyprogesterone acetate (Prempro®)
- FDA believes that findings of the WHI study apply to all ET/HT combinations

WHI – Fracture, CAD
WHI – Cancer Data

- Colorectal Cancer
- Invasive Breast Cancer

WHI limitations
- Looked at 0.625 mg qd EE and 2.5 mg MPA
- Not investigated other formulations
- No distinction between estrogen and progestin
- Transdermal application?

ET/HT – FDA Recommendations
- ET/HT IS approved to PREVENT osteoporosis
- Consider non-estrogen preparations first
- “smallest dose for shortest time”
- Weigh benefit and risks (DVT, CAD, breast cancer)

Teriparatide = PTH (1-34)
- First 1-34 aminoacids of the PTH molecule
- SQ QD
- Max use for 2 years
- Decreases vertebral AND non-vertebral fractures after mean 18 months treatment

Teriparatide Indications
- LOW TURNOVER bone disease!
- Postmenopausal women osteoporosis
- Men
  - Primary osteoporosis
  - Hypogonadal osteoporosis
- High risk
  - Previous osteoporotic fracture
  - Multiple risk factors
  - T-score < -3
  - Intolerant to other therapies

Teriparatide Warnings
- Hypercalcemia
- Paget’s disease
- Children / adolescents
- Pregnancy
- Bone cancer (esp. osteosarcoma)
- Cancer history (esp. with bone metastasis potential) or radiation to bone
**RANKL/RANK/OPG System**

**Real-World Obstacles in the Management of Osteoporosis**

- Insufficient rates of diagnosis
- Low awareness of the necessity to treat
  - Low persistence: patient stops taking medication
  - Poor compliance: patient does not follow dosing instructions

**Probability of fracture in 24 months in bisphosphonate-treated patients**

MPR = medication possession ratio

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**“Bones of Glass and a Heart of Stone”**

**Aortic Calcifications and Bone Loss**

- **157 women**
- Quantiles: 1st, 2nd, 3rd, 4th
- Statistical significance: P = 0.002

**Coronary Calcifications and Bone Volume**

- **38 dialysis patients**
- Probability of fracture (100) vs BV/TV
  - Probability of fracture vs BV/TV
  - Statistical significance: P = 0.001
Conclusion

- Osteoporosis pervasive health problem of major proportions incurring enormous healthcare expenditures
- Underdiagnosed and undertreated
- Different types of bone loss requires different therapeutic approaches
- Therapies for high turnover might be harmful to patients with low turnover.
- Prevention and treatment of osteoporosis not only desirable for prevention of fractures but possibly also for slowing progression of vascular calcifications