Osteoporosis in Men
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Why do men fracture?
Diagnostic work-up
Testosterone
Osteoporosis therapies
Sleep

Risk factors for hip fracture in men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.3 (1.6, 2.4)</td>
</tr>
<tr>
<td>FN BMD</td>
<td>2.6 (2.0, 3.7)</td>
</tr>
<tr>
<td>Falls</td>
<td>3.1 (2.5, 3.8)</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>2.3 (1.6, 3.0)</td>
</tr>
<tr>
<td>Height loss</td>
<td>1.3 (1.2, 1.5)</td>
</tr>
<tr>
<td>Tricyclic use</td>
<td>2.9 (1.4, 6.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2.8 (1.3, 6.2)</td>
</tr>
<tr>
<td>Parkinson's</td>
<td>1.5 (1.3, 2.0)</td>
</tr>
<tr>
<td>Cognition</td>
<td>1.4 (1.1, 1.8)</td>
</tr>
</tbody>
</table>

5994 men age >65 yrs
Follow-up 8.6 yrs
178 hip fractures

Hip fracture as a function of BMD

Study of Osteoporotic Fractures
N=8065, hip fracture/5yrs N=245
46% of hip fracture BMD T score < -2.5
Wainwright et al. JCEM 2005

Men with major osteoporotic fractures usually do not have “osteoporotic” BMD

- BMD from DXA predicts fracture risk in men
- The association between BMD is similar in men and women

Cummings et al. JBMR 2006

Risk of falls:
- Muscle mass and function
- Balance and coordination

Bone strength:
- Trabecular density
- Cortical density
- Cortical thickness
Physical performance and risk of hip fractures in older men

Hazard ratio (95% CI) of hip fracture

<table>
<thead>
<tr>
<th>Test of physical performance</th>
<th>Age adjusted</th>
<th>Multiply adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated chair stands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable</td>
<td>12.6 (4.1-38.9)</td>
<td>8.2 (2.7-25.0)</td>
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<tr>
<td>Quartile 4 (worst)</td>
<td>4.7 (1.1-12.3)</td>
<td>3.6 (1.4-9.4)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>3.0 (1.1-8.2)</td>
<td>2.7 (1.0-7.3)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.8 (0.6-5.4)</td>
<td>1.6 (0.6-4.7)</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Walking speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (worst)</td>
<td>3.0 (1.4-6.7)</td>
<td>2.4 (1.1-3.4)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.4 (0.6-3.3)</td>
<td>1.3 (0.6-3.1)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.9 (0.3-2.5)</td>
<td>0.9 (0.3-2.3)</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
</tbody>
</table>

* Age, clinical center, FN/BMD, BMI, hx of MI, hx of stroke

The contribution of activity and physical performance to the frequency of falls in older men

2741 men (78.8±5 years; range 71-98)
Activity monitoring 5-7 days
Multiple physical performance measures

Tissue thickness and hip fracture risk in older men

70 men with incident hip fracture and 222 non-fractured controls, all with DXA and QCT finite element analysis
Tissue thickness was minimally lower in hip fx vs controls (29 vs 31 mm, p=0.2)(lower in trochanteric fx – 26 mm)
Tissue thickness was not associated with hip fracture risk (RR 1.0 0.8-1.3)
Tissue thickness was considerably lower in men than previously reported in women (69 vs 31 mm; Bouxsein el at JBMR 2007).
Attenuation of fall force greater in women (61% vs 27%)

The rate of BMD loss accelerates with age in most, but not all, men

Heterogeneity of loss
- 24% no loss/gain
- 63% “expected” loss
- 13% accelerated loss (at least 1 SD greater than mean loss)

Fracture risk is higher in men with greater BMD loss

Adjusted rate of non-spine and hip fracture per 100 person years, by category of BMD change and tertile of baseline BMD

- Should men with low normal BMD (not yet in the range requiring treatment) routinely have a repeat measure in ~2-3 yrs?
- Should men with the greatest rate of bone loss be treated earlier?
Estimated time for 10% to develop osteoporosis:
- 8.5 years (95% CI=6.7, 10.9) for those with lowest T-score ≤ 1.50.
- 8.7 years (95% CI=2.1, 3.4) years for those with lowest T-score 1.50 to 1.99.

MrOS. 5,415 community-dwelling men aged ≥65 years without hip or clinical vertebral fracture or antifracture treatment. Follow-up between 2000 and 2009.

Osteoporosis in Men

Diagnostic work up

Etiologies
- Genetic
- Secondary
- Idiopathic

Genetic Disorders

Osteogenesis imperfecta (multiple genes): 80/10,000
- Many cases may be unrecognized because of mild disease
- Type I (collagen 1A1, 1A2) most likely to present as “osteoporosis” - usually includes a history of fractures in childhood
- Other phenotypic features (e.g. blue sclera, scoliosis, hearing loss)

Marfan Syndrome (fibrillin): 5/10,000 people
- Higher rate of fracture, lower BMD (Moura et al Joint Bone Spine 2006)
- Characteristic physical findings

Ehlers Danlos
- Lower BMD
- Joint/skin laxity

Estrogen receptor or oestrogenase mutations:
- Normal virilization
- Open epiphyses
- Forme fruste presentation as osteoporosis?

Genotyping is appropriate when the clinical presentation is suggestive.

Secondary Osteoporosis in Men

Alcoholism
Endocrine disorders
Hypogonadism
Cushing’s syndrome
Diabetes (type 1 and 2)
Hyperthyroidism
Hyperparathyroidism (primary or secondary)
Gastrointestinal disorders
Malabsorption Syndromes
Primary biliary cirrhosis
Post gastrectomy syndromes
Chronic obstructive pulmonary disease
Organ transplantation osteoporosis
Immobilization
Neuromuscular disorders
Hypercalcemia

Systemic Illnesses
Mastocytosis
Rheumatoid arthritis
Multiple myeloma
HIV disease
Various other malignancies
Medication/drug-related
Glucocorticoids
Androgen deprivation therapy
Selective serotonin reuptake inhibitors
Anti-convulsants
Chemotherapeutics
Thiazolidinediones
Thyroid Hormone (when used in excess)

History and Physical Exam
Targeted laboratory testing
Screening laboratory testing

It is important to identify these conditions so they can be treated.
Osteoporosis in Men: the Value of Laboratory Testing

Ryan, Petrov, Adler Osteoporosis Int 2011

- Retrospective chart review of 234 men referred to a metabolic bone clinic for osteoporosis as a result of DXA screening; mean age was 70.6 years.
- Screening chemistries, 25-hydroxyvitamin D, testosterone, bone turnover, follicle-stimulating hormone, thyroid-stimulating hormone, and spot urinary calcium-to-creatinine ratio.
- Secondary osteoporosis in 75%. Many known at the time of referral.
- New diagnoses by lab tests in “50%, almost all due to hypogonadism or vitamin D deficiency.

In referral patients or groups with a higher burden of chronic disease, the number of conditions associated with bone/mineral disturbance is high.

In community based men identified by screening, the prevalence of potential risk factors is also high, but often not more prevalent than in unaffected men

- Are the conditions related to the causation of the osteoporosis?
- Does treatment of these conditions improve outcomes?
- Is testing cost-effective?

Osteoporotic Fractures in Men (MrOS) Study

Fink et al Osteoporosis Int 2016

- 1572 men with both BMD and laboratory measures available, 10.4% (n=163) met criteria for osteoporosis (T-score ≤−2.5 at total hip, femoral neck, or lumbar spine using a male reference database).
- Of the 163 men with osteoporosis, 58.3% had at least one of several laboratory abnormalities postulated as potential secondary factors:
  - 30.7% with 25(OH)D <20 ng/mL
  - 17.1% with kidney disease
  - 10.5% with TSH >0.55 mIU/L
- Men with osteoporosis were not significantly more likely than men without osteoporosis to have any of these laboratory abnormalities, except for high alkaline phosphatase or 25(OH) vitamin D insufficiency (<50 ng/mL).

Evaluation of Osteoporosis in Men

- 1.4.1. We suggest measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25(OH)D, total testosterone, complete blood count, and 24h urinary calcium (creatinine and sodium) excretion in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents. (low quality evidence)
- 1.4.2. If history or physical examination suggest a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free and light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and PTH levels. (low quality evidence)

Idiopathic Osteoporosis in Men

Incidence perhaps 0.4/100,000 (Khosla et al Bone 1994)

Variable characteristics:
- Age (20-60 yrs)
- Clinical severity (IF fractures, severity of BMD deficit)
- Levels of remodeling markers - usually normal

Biochemical etiology unclear; probably heterogeneous.

- Poor peak bone mass development
- "There is no specific test for idiopathic osteoporosis. Definition: when no secondary cause is identified.
- It is a diagnosis of exclusion."
Osteoporosis in Men

Testosterone
- Hypogonadism has adverse effects on bone development during adolescence, and bone density/strength in adulthood
- Effects on bone in adults - estradiol >> testosterone

Androgens

Aromatase

Estrogens

Low testosterone is associated with increased fall risk

Hypogonadism has adverse effects on bone development during adolescence, and bone density/strength in adulthood. Effects on bone in adults - estradiol >> testosterone.

The T Trials

Eligibility criteria included an age of 65 years or older and serum testosterone levels that averaged less than 275 ng per deciliter.

The limited clinical utility of testosterone, estradiol, and sex hormone binding globulin measurements in the prediction of fracture risk and bone loss in older men

Results the same for hip fracture and shorter follow-up times

Sex steroids and bone in men
- Sex steroids, especially estradiol, are important for the maintenance of skeletal integrity in men.
- In men with severe hypogonadism (androgen deprivation therapy) the risk of bone mass and fractures is clearly higher.
- Measure BMD and assess risk factors.
- Preventive and therapeutic treatment is appropriate.
- In men who present for osteoporosis evaluation, significantly low testosterone levels are unlikely.
- Measure testosterone levels if there is a clinical suspicion that significant hypogonadism is present.
- Therapy with testosterone is likely to increase BMD in men with low T.
- Should T be used for osteoporosis in men?
  - Fracture data are not available (reduce falls? Improve bone strength?)
  - Testosterone therapy for osteoporosis in hypogonadal may be appropriate in men under certain circumstances.
  - When T therapy is indicated for other reasons.
  - When fracture risk is modest.
- In hypogonadal men at high fracture risk who don’t have indications for T, anti-osteoporosis drugs are appropriate.

The T Trials

Effect of Testosterone Treatment on Volumetric Bone Density and Strength in Older Men With Low Testosterone: A Controlled Clinical Trial

No fracture trials with testosterone.
No controlled data on long term adverse effects.

Snyder et al JAMA Internal Med. 2017
Osteoporosis in Men

Osteoporosis therapies

Treatment of osteoporosis in men

Anti-resorptives
Bisphosphonates
Denosumab

Anabolics
Teriparatide
Abaloparatide

Pending
Anti-sclerostins

Alendronate therapy in osteoporotic men
Percent change in lumbar spine BMD and vertebral fracture incidence after 2 years of alendronate 10 mg/day in 241 men with low BMD

Effects on BMD with other bisphosphonates in the treatment of men with low BMD - very similar to those in women
Residronate
Ibandronate
Zoledronate

Results with denosumab in the treatment of men with low BMD - very similar to those in women
Beneficial effects in men treated with teriparatide very similar to those in women

Zoledronate treatment in men reduced the rate of new radiographic vertebral fractures

Treatment of osteoporosis in men

• Although most trials in men have been small and designed to evaluate BMD change rather than fracture rates, the effects of drug therapies in men have been very similar to those in women

• No a priori reason to believe osteoporosis drugs should be less effective than in women

• Evaluate and treat men using methods the same as in women
  • Exception – broad BMD screening in men >70 years
The US Preventive Services Task Force (2011) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

American College of Physicians (2017) ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk of vertebral fracture in men who have clinically recognized osteoporosis.

Endocrine Society (2012) We recommend pharmacological therapy for men at high risk for fracture including, but not limited to:
- Men who have had a hip or vertebral fracture without major trauma.
- Men who have not experienced a spine or hip fracture but whose BMD of the spine, femoral neck, and/or total hip is 2.5 SD or more below the mean of normal young white males.
- In the United States, men who have a T-score between 1.0 and 2.5 in the spine, FN, or TH plus a 10-yr risk of experiencing any fracture 20% or 10-yr risk of hip fracture 3% using FRAX.
- Men who are receiving long-term glucocorticoid therapy in pharmacological doses (e.g., prednisone or equivalent 7.5 mg/d), according to the 2010 guidelines of the American Society of Rheumatology.

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Obstructive sleep apnea
- Obstructive sleep apnea (OSA) affects nearly one in seven adults, many of whom are undiagnosed.
- OSA predominantly affects older, obese, males; some studies suggest that up to one in four older men are affected.
- OSA has been associated with impaired motor function, cognitive function, and memory, which contribute to an increased risk of falls and accidents.
- Apneic events cause hypoxia and recurrent, apparently life-saving arousals that result in marked elevations in sympathetic nervous system (SNS) activity, which is often sustained beyond sleep throughout the waking hours.
- OSA is linked to increased inflammation. Hypoxia?
- In OSA, sleep restriction and disruption contribute to disorganized sleep architecture, disordered sleep-wake homeostasis, and subsequent disturbances in normal hormonal rhythms.

Disordered sleep and bone

Bone Turnover Markers After Sleep Restriction and Circadian Disruption in Humans: A Mechanism for Sleep-Related Bone Loss
- Thus far, studies of sleep disturbance and BMD have been cross sectional and conflicting.
- Some have shown increased bone turnover in those with sleep apnea.
- Some have shown lower BMD.
- Similarly, studies of sleep disturbance and fractures have been underpowered and conflicting.

Clock genes, which have been identified in virtually all cells (Per1, Per2, Cry1, Clock, and BMAL1), contribute to the rhythmicity of numerous physiological systems.
- The intrinsic central, or master, circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN receives light/dark cycle input to synchronize its own activity and thereby orchestrate behavioral, physiological, and cellular rhythms.
- The SCN communicates and synchronizes with clock genes located centrally and in the periphery via direct neural connections, the SNS, hormonal signals (such as melatonin and cortisol), and the regulation of body temperature.

Swanson et al. JBMR 2015

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