Bone disease in women with HIV

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Outline

• Definitions
• Low bone density in HIV+ persons
• Fracture risk in HIV+ persons
• Investigations
• Management options
Definitions

- T-score is the number of standard deviations below the mean bone mineral density (BMD) for healthy, young, sex-matched population
- In postmenopausal women and men aged $\geq 50$ years osteoporosis is diagnosed by T-score $\leq -2.5$ or fragility fracture of the hip or spine
- This definition should not be used for other patient populations
- T-score $\leq -2.5$ was chosen to capture 30% of postmenopausal Caucasian women with lowest BMD and approximates lifetime risk of fragility fracture in that population
- For young people Z-score $\leq -2$ is abnormal (or below expected for age) but should be interpreted in the context of fracture risk
- These definitions are important as the vast majority of research of bone disease in HIV has been done in young men
Do HIV+ people have low BMD?

- **Increased prevalence of traditional risk factors**: low body mass index (BMI), glucocorticoids, comorbidities, HCV/liver disease, early menopause, smoking

- **HIV infection**: elevated levels of inflammatory cytokines resulting in bone loss

- **Antiretroviral treatment**: increases bone turnover and initially resorption > formation

  - Tenofovir: renal phosphate wasting
  - Efavirenz: potentiates conversion of 25-OH vitamin D to inactive metabolite
Do HIV+ people have low BMD?

- A study of peak BMD in HIV+ people age 20-30 years found no difference compared to controls.
- A meta-analysis of longitudinal studies concluded that initiation of ART is associated with accelerated bone loss lasting about a year that is followed by sustained stability/increase.
- Patients reached nadir BMI 9 months after ART initiation and then began to gain weight.
Do HIV+ women have low BMD?

- Prospective cohort study of 92 HIV+ and 95 HIV- postmenopausal Hispanic and African-American women, important to note that controls were patients at medicine clinic

- HIV+ had adjusted (slightly but significantly) lower BMD at the spine and total hip and this was associated with elevated bone turnover markers

- In HIV+ women BMD did not differ between those taking ART and those who were not

- In a subset of the above cohort followed longitudinally, HIV+ was associated with slightly more bone loss in lumbar spine (adjusted) at one year, but no difference at other sites

- Tenofovir was associated with more bone loss

- No difference in self-reported fracture or radiographic vertebral fracture

- These are the only studies investigating low BMD specifically in postmenopausal women with HIV

J Clin Endocrinol Metab 2012; 97: 554

J Clin Endocrinol Metab 2010; 95: 620
Do HIV+ people have low BMD?

- Most of the research has been done in young men which can make it difficult to interpret.
- There is little agreement between studies regarding effect HIV-specific risk factors: effect of certain medications, AIDS-defining illness, CD4 nadir.
- Many reasons to be concerned that HIV+ people have lower BMD, including an increased prevalence of traditional risk factors, and more studies are needed in high risk populations, particularly older women.
Are HIV+ people at increased risk of fracture?

- Population-based retrospective case control in Spain, over age 40, 75% male, 2007-2009
- Not controlled for ART
- Age and sex-adjusted hazard ratio for hip fractures 6.2 and all major (hip, clinical spine, pelvis, tibia, multiple rib, proximal humerus, wrist/forearm) fractures 2.7 – this may be more meaningful than adjusted HR as patients cannot be separated from confounders

Figure: Age-specific fracture incidence rates (per 100 person-years) in HIV-infected versus uninfected patients
Are HIV+ people at increased risk of fracture?

- All Danish HIV patients over age 16 and population-based controls, mostly male, 1995-2010

- Overall fracture incidence rate ratio: HIV+ 1.3, HIV and HCV+ 2.9 per 1000 person-years (HCV known to correspond with injection drug and alcohol use in this cohort)
Are HIV+ people at increased risk of fracture?

- Large medical-system database retrospective case-control examining hip, wrist, vertebral fractures, 1996-2008

- Overall prevalence of fractures per 100 people was 2.87 (HIV+) vs. 1.77 (controls) or 60% higher prevalence in HIV+ people

Left: women, right: men

J Clin Endocrinol Metab 2008; 93: 3499
Are HIV+ women at increased risk of fracture?

- No studies of fractures in exclusively postmenopausal HIV+ women
- Population-based controlled observational study in Canadian women, mean age 38 years, showed:
  - OR for self-reported lifetime prevalence of low trauma fracture 1.7 (1.1-2.6)
  - Young women who may have had risk factors for both HIV and fractures
  - BMD did not differ between cases and controls
Are HIV+ women at increased risk of fracture?

- Prospective case (1728 HIV+ women, 66% taking ART) control (663 clinic-based) study of non-Caucasian, mostly premenopausal women, followed 2002-2008

- HIV+ women were older (40 vs. 36 years), more likely to be postmenopausal, and had lower, but still elevated, BMI (28.5 vs. 30,) BUT they were more likely to be on HRT, calcium, and/or vitamin D, and less likely to be smokers

- No difference in incident fractures or incident fragility fractures

- HIV+ was not associated with an increased risk of fracture in multivariate analysis, traditional risk factors were predictive of fracture

- Conclusion: HIV+ people are probably at increased risk of fracture but there is limited data for persons at high-risk of LOW TRAUMA fracture (particularly older women.) Whether the increased risk is associated with HIV itself, or an increased prevalence of traditional risk factors for low BMD and fracture, remains unclear and may be less relevant in the treatment of individual patients

Osteoporos Int 2007; 18: 1345
AIDS 2010; 24: 2679
Is your patient at increased risk of fracture?

• History, physical examination, BMD testing

• National Osteoporosis Foundation recommends osteoporosis screening with DXA BMD testing

  • for all women aged 65 years and men aged 70 years, regardless of clinical risk factors

  • for adults aged 50 years who sustain a fracture

  • for younger postmenopausal women and men aged 50–69 years if there is concern for osteoporosis based on their clinical risk factor profile (traditional risk factors, ART, etc.)

Is your patient at increased risk of fracture?

Secondary osteoporosis “Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease”
What other testing should be done in patients with osteoporosis/elevated fracture risk?

• Corrected calcium – to screen for primary hyperparathyroid
• Creatinine
• ALP
• CBC
• TSH
• 25-OH vitamin D - after appropriate supplementation for 3-4 months
What other testing should be done in patients with osteoporosis/elevated fracture risk?

- 24 hour urine collection for calcium (to evaluate for low intake or absorption)
- 24 hour urine collection for phosphate (if patient is taking tenofovir)
- SPEP, UPEP in the setting of vertebral compression fractures
- PTH
- Celiac antibody screening
- Gonadal function
- Thoracic and lumbar spine radiographs
How to manage HIV+ patients with increased fracture risk?
What about supplements?

- They are having a bad year…

Much of the criticism is probably justified but it’s important to remember that randomized controlled trials of supplements tend to enroll healthy, well-nourished participants.
Calcium supplementation

• IOM recommendations: total daily calcium 1200 mg for women over age 50, 1000 mg for others

• Generally meta-analyses do not provide much support for a reduction in fracture risk with calcium supplementation or high dietary calcium

• There is evidence for a reduction in fracture risk with calcium and vitamin D supplementation in institutionalized elderly

• A LARGE prospective cohort study of calcium intake in older Swedish women:
  • Compared to median intake (882-996 mg daily), dietary calcium below 750 mg daily was associated with an increased risk of any fracture and of hip fracture.
  • Higher intake (>1137 mg daily) was not associated with increased benefit and was associated with increased risk of hip fracture


BMJ 2011; 342: d1473
Calcium supplementation - possible adverse effects

• In large meta-analyses calcium supplementation has been associated with a 25-30% relative increased risk of MI (low absolute risk and wide confidence interval)

  • The same group had recently conducted a placebo controlled 5-year RCT of calcium supplementation in older women that also showed this association (prespecified secondary endpoint)

• We do not have a good explanation for this finding
Calcium supplementation

• There is no substitute for a healthy diet

• Our old (and current) recommendations likely reflect data from a population deficient in vitamin D. North American recommendations for daily intake for older women are quite high compared to European recommendations, about 1200 mg vs. 800 mg

• There is evidence that a daily intake of about 900 mg daily is sufficient

• Try to ascertain dietary calcium intake and recommend appropriate dietary calcium before recommending high dose supplementation
Vitamin D supplementation

• IOM recommends vitamin D 600 IU daily for everyone except for women over 70 - 800 IU daily, target vitamin D level 30-50 ng/mL and these are probably reasonable recommendations for HIV+ people as well

• Benefits:
  
  • Enhances GI absorption of calcium
  
  • May improve muscle strength
  
  • May have positive effect on balance and decrease the risk of falls
  
  • May reduce risk of fracture

• Patients will ask about other benefits of vitamin D supplementation or may be taking large doses because of perceived benefits

• Currently there is insufficient evidence to conclude that vitamin D prevents/improves outcomes in cancer or CVD

• Epidemiological evidence in inconclusive

• VITAL (the VITamin D and OmgegA 3 TriaL) aims to answer this question


Vitamin D supplementation

Several studies suggesting high prevalence of deficiency in HIV+ people but many are not controlled.

Prospective observational cohort of HIV+ patients, who were not on D supplements, using control data from NHANES participants.

Defined D deficiency as < 20 and insufficiency as < 30 ng/mL.

HIV+ 70.3% were insufficient or deficient vs. 79.1% of general population (significant difference), age, race, and sex adjusted.

The only HIV-related risk factor for D deficiency was treatment with efavirenz.
Other supplements

- Other supplements that patients often ask about...
  - Magnesium – Western diets are not magnesium deficient, supplementation not routinely recommended
  - Vitamin K – largest RCT showed no improvement in BMD but a trend toward decreased incidence of fracture, need larger multi-centre trial
  - Strontium – the only salt available in North America is strontium chloride whereas strontium ranelate is the salt available in Europe for which there is some favourable evidence
What are the pharmacologic options in HIV?

- The only evidence is for bisphosphonates
  - zoledronic acid was shown to increase BMD at all sites vs. placebo at 2 years in 43 men
  - alendronate increased BMD at lumbar spine and total hip vs. placebo at 1 year in 82 patients, 29% women
  - both trials enrolled young patients whose fracture risk was not high
  - neither trial was designed to study fractures
- Teriparatide
  - No data
- Denosumab
  - No data and not recommended as RANK/L has role in immune regulation

J Clin Endocrinol Metab 2007; 92: 1283
AIDS 2007, 21:2473
The Journal of Infectious Diseases 2012; 205: S391
Bisphosphonates and atypical femur fractures

Table 3. ASBMR Task Force 2013 Revised Case Definition of AFFs

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.

In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

Major features
- The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
- The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
- The fracture is noncomminuted or minimally comminuted
- Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Minor features
- Generalized increase in cortical thickness of the femoral diaphyses
- Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral incomplete or complete femoral diaphysis fractures
- Delayed fracture healing

Changes are in bold.

ASBMR = American Society for Bone and Mineral Research; AFF = atypical femur fracture.

*Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget’s disease, fibrous dysplasia).
Bisphosphonates and atypical femur fractures

- 3.2-50 atypical femur fractures per 100,000 person years (rare)
- BUT relative risk on bisphosphonates ranges from 2.1 to 128
- Risk may increase significantly with exposure to BP > 3 years
- There seems to be a significant association with glucocorticoids
Conclusion

- As women with HIV are living into old age they may be increasingly affected by low bone density and fracture.
- More research is needed in this patient population to define the scope of the problem and to develop treatment options and strategies.