Osteoporosis management in premature ovarian failure and women under age 60

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Definitions

• “Osteoporosis may be diagnosed in postmenopausal women and in men age 50 and older if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less:

  – Reference group:
    • Manufacturers should continue to use NHANES III data as the reference standard for femoral neck and total hip T-scores.
    • Manufacturers should continue to use their own databases for the lumbar spine as the reference standard for T-scores
    • If local reference data are available they should be used to calculate only Z-scores but not T-scores.”

2015 International Society of Clinical Bone Densitometry Official positions-Adult
Osteoporosis

- Minimal trauma fracture (not digits)
- AND/OR
- BMD ≤ -2.5 in PM and perimenopausal women and men over 50
- Low trauma fracture – standing height or less with absence of major trauma

Figure 1. Distribution of bone mineral density in healthy women aged 30–40 years

John A Kanis
Diagnosis of osteoporosis and assessment of fracture risk
http://dx.doi.org/10.1016/S0140-6736(02)08761-5
Figure 3. Remaining lifetime risk of hip fracture in women aged 50 years, according to bone mineral density (BMD) or T score at the hip.

Fracture risk vs age by femoral neck BMD

Cummings JAMA 2002
Fracture risk vs age by femoral neck BMD

When to test BMD

2015 ISCD Official Positions-Adult
- Women ≥ 65 y
- Postmenopausal or perimenopausal women < 65y with another risk factor
  - Low BMI
  - Prior fracture
  - Medication or disease known to cause bone loss
- Fragility fracture
- To monitor response to therapy

Cummings JAMA 2002
Premenopausal OP

• Not by BMD alone
• In premenopausal women use Z-score with score ≤ -2.0 “below expected range for age” (not same assoc between BMD and fracture in young people)
• Low bone density for age (Z-score ≤ 2.0) plus a risk factor for fracture or a secondary cause of OP

Premenopausal OP: Causes

• Estrogen deficiency
  – Primary ovarian failure
  – Other causes of amenorrhoea: low body weight, eating disorder, hyperprolactinaemia, hypopituitarism
  – Iatrogenic: oophorectomy, chemotherapy, aromatase inhibitors
Figure 3 Function and signalling mechanisms of ERα and AR in female and male mammals


Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: Results from the Study of Women’s Health Across the Nation (SWAN)

Journal of Bone and Mineral Research
Volume 27, Issue 1, pages 113-118, 22 Dec 2011 DOI: 10.1002/jbmr.534
Premature menopause (<40y)

- Spontaneous primary ovarian insufficiency
- Surgical - the worst bone outcomes
- Chemotherapy related

Bone in POI

- In a study of 442 women with spontaneous POI, compared to controls, BMD 2-3% lower at spine and hip
- Factors associated with low bone for age:
  - Low vitamin D
  - Delay in diagnosis > 1 yr
  - Not using estrogen therapy
  - Low dietary calcium
  - Sedentary lifestyle

Popat et al, J Clin Endocrinol Metab. 2009;94(7):2277
Figure 1. Bone mineral density (BMD) of the primary ovarian insufficiency (POI, N = 32) and premenopausal reference (N = 25) groups. A, L1-L4 lumbar bone mineral density (*P = 0.040; Student t-test). B, Femoral bone mineral density.

Premenopausal OP: Causes

- Medications
  - Glucocorticoids
  - Prolonged use of depot medroxyprogesterone acetate (estrogen deficiency)
  - Methotrexate
  - Some chemotherapy agents
  - Prolonged use of heparin eg in pregnancy
  - Anti epileptics (eg. Carbamazepine - CYP450 catabolism of vitamin D)
  - ?loop diuretics ?TCAs/SSRI ?PPI
Premenopausal OP: Causes

• Systemic illnesses
  – Coeliac disease
  – Hyperthyroidism
  – Inflammatory bowel disease
  – Cystic fibrosis
  – Osteogenesis imperfecta
  – Hyperparathyroidism
  – Immobilisation eg spinal cord injury

Premenopausal OP: Causes

• Other risk factors
  – Smoking: pack/day reduces BMD 5-10% over a lifetime
  – depression
Premenopausal OP: Causes

- Pregnancy – decrease in BMD in some studies
- Lactation
  - Approx 5% reduction in BMD over 6 months
  - More pronounced with longer duration
  - PTHrP secreted by breast/estrogen deficiency
  - Recovery of BMD may take 18 months, depending on resumption of menses


Pregnancy and Lactation Associated OP

- Fractures in late pregnancy/early post partum
- Usually first pregnancy, rarely recurs
- ?excessive pregnancy bone loss ?other secondary cause ?genetic susceptibility
Premenopausal OP: Causes

- Idiopathic – everything else ruled out
- ?significance of isolated low BMD

Treatments

- Exercise:
  - a small but significant effect in pre and postmenopausal women
  - Decreased fracture risk in older women
  - ET + exercise increases BMD in premature menopause more than ET alone  
  

- Cochrane review 2011 (postmenopausal women)
  - Strength/resistance training best for neck of femur BMD
  - Combination exercise best for spine BMD
Calcium and vitamin D

- Still controversial
- Aim for most calcium intake from dietary sources
- WHI >35,000 women randomized to Ca 1000mg + vit D 400IU or placebo
  - No difference in MI
  - At 7 yrs hip BMD 1.06% higher in CaD group vs placebo group
  - Decreased risk of hip fracture (HR 0.71, 95% 0.52-0.97) IF compliant (>80%)
  - Increased risk of kidney stones (HR 1.17, 95% CI 1.02-1.34).


Premature menopause

- Estrogen therapy the mainstay of treatment
- HRT (not contraceptive)
- OCP
Bone Mineral Density in Young Women With Primary Ovarian Insufficiency: Results of a Three-Year Randomized Controlled Trial of Physiological Transdermal Estradiol and Testosterone Replacement

Figure Legend:
A, Mean (SEM) percentage change from screening in the femoral neck BMD. B, Mean (SEM) percentage change from screening in the lumbar spine BMD.
Cartwright et al, J Clin Endocrinol Metab, 2016, 101(9):3497–3505

Figure 1. Percentage of women with POI without treatment (n = 107) or using standard dose HT (n = 132) with normal or compromised (osteopenia or osteoporosis) lumbar spine bone mineral density.

Chi squared Test $P = 0.0163$

Figure 1. Percentage of women with POI without treatment (n = 107) or using standard dose HT (n = 132) with normal or compromised (osteopenia or osteoporosis) lumbar spine bone mineral density.
After breast cancer

- Impact and resistance training increases BMD at the hip, and reduces BMD loss at the spine in breast cancer survivors with premature menopause
  Winters-stone KM, et al Osteoporosis Int. 2013 May;24(5):1637-46

- Zoledronic acid every 3 months improves BMD in premenopausal women with bone loss
  Kalder, M et al Osteoporosis Int. 2015 Jan;26(1):353-60
After breast cancer

• Risedronate prevents decline in BMD in postmenopausal women on anastrazole

• Denosumab reduces fracture risk in postmenopausal women on aromatase inhibitors
  Gnant et al. Lancet. 2015 Aug 1;386(9992):433-43

Eating disorders

• Hormone therapy not effective for improving bone density in anorexia nervosa

• Improvements in BMD occur with increase in body weight and resumption of menses
Idiopathic premenopausal OP

- No much data
- Ca/D
- Exercise
- Smoking cessation
- Consider estrogen if amenorrhoea
- Consider bisphosphonate if fractures

Premenopausal OP-other

- Treat secondary causes rather than use antiresorptives eg coeliac disease
- Osteogenesis imperfecta - bisphosphonate
Postmenopausal women < 60y

- Lots of guidelines but often difficult
- Fragility fracture
- Postmenopausal and T-score ≤ -2.5
- FRAX 10 year risk of hip fracture ≥ 3%
- FRAX 10 year risk of any fracture ≥ 20%
- (antiresportives generally reduce fracture risk by 50% but treatment based on fracture risk assessment not evaluated in RCTs)

When whether to treat is not clear...

- use bone turnover markers to further clarify risk
BTMs Predict Fracture Independently of BMD

EPIHOS prospective cohort study of 7598 healthy women; age 75+ yrs

Hip Fracture Risk (OR)

- Low Hp BMD: 2.7
- High CTX: 2.2
- Low Hp BMD & High CTX: 4.8


IOF-IFCC Recommendations

- An increase in BTM concentration predicts fracture risk independently of BMD and prior fracture

- More data needed before routine clinical use can be recommended
  - Which marker?
  - What threshold?
  - How to combine with other risk assessment approaches e.g., FRAX?

- BTMs widely adopted in monitoring treatment. Application limited by:
  - Inadequate appreciation of sources of variability
  - Limited data on comparison of treatments using the same BTM
  - Inadequate quality control.
Risks of antiresportives

- Reflux/oesophagitis with oral bisphosphonates
- Flu-like symptoms w IV zoledronic acid (1/3 with first infusion)
- Osteonecrosis of the jaw – risk 1:10,000-1:100,000 in postmenopausal women taking oral bisphosphonates for OP
- Atypical femoral fractures rare with long term use (3-50 cases per 100,000 person-yrs, maybe more with longer duration). Prodrome, bilateral
Duration of treatment

- Oral bisphosphonate
  - 5 years if low risk (no fracture, T score >-2.5)
  - 10 years if high risk
- IV zoledronic acid
  - 3 years if low risk
  - 6 years if high risk
- ?when resume ?if significant decline in BMD or rise in bone turnover markers

Duration of treatment

- Teriparatide – PTH for severe OP, with fracture on bisphosphonate
- Small studies in younger women, even as first line therapy