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

2015 International Society of Clinical Bone Densitometry Official positions-Adult

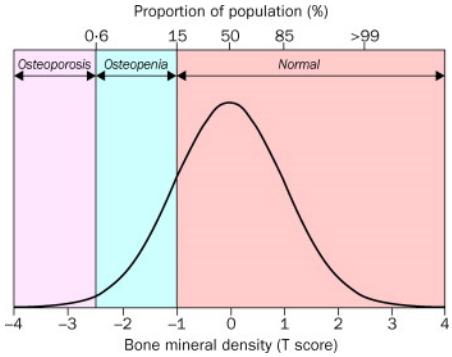


Figure 1. Distribution of bone mineral density in healthy women aged 30–40 years

John A Kanis
Diagnosis of osteoporosis and assessment of fracture risk
null, Volume 359, Issue 9321, 2002, 1929–1936
http://dx.doi.org/10.1016/S0140-6736(02)08761-5

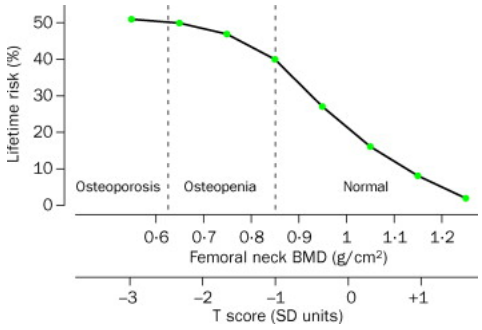
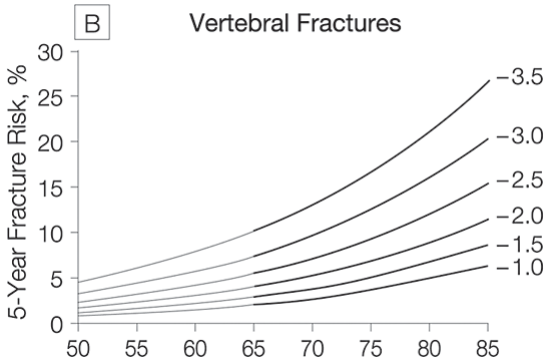


Figure 3. Remaining lifetime risk of hip fracture in women aged 50 years, according to bone mineral density (BMD) or T score at the hip

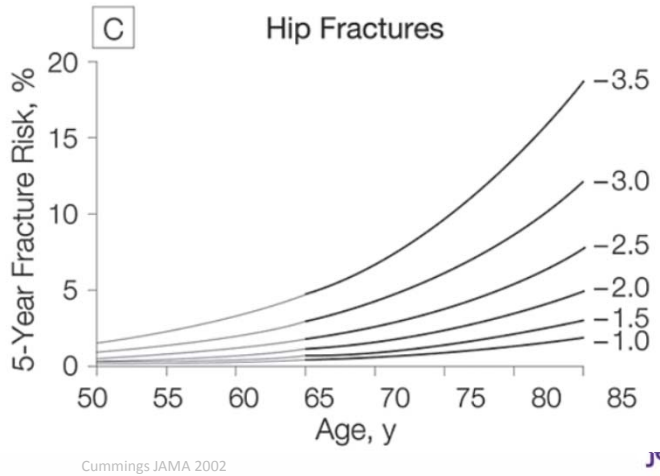
John A Kanis, **Diagnosis of osteoporosis and assessment of fracture risk** null, Volume 359, Issue 9321, 2002, 1929–1936, http://dx.doi.org/10.1016/S0140-6736(02)08761-5

Fracture risk vs age by femoral neck BMD



Cummings JAMA 2002

Fracture risk vs age by femoral neck BMD



Cummings JAMA 2002

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

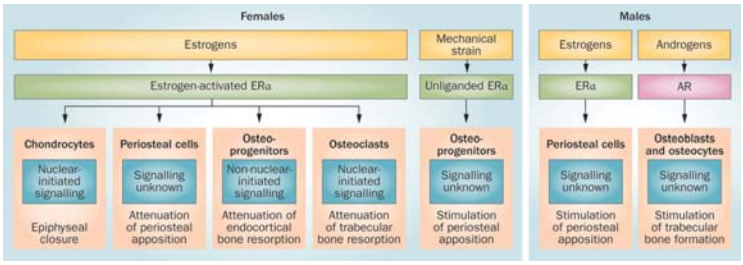
Premenopausal OP

- 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

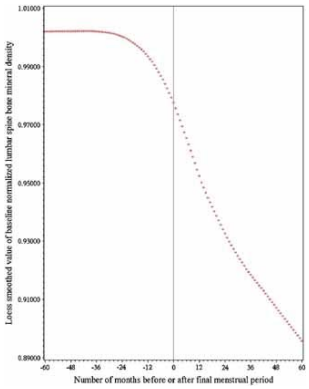
Figure 3 Function and signalling mechanisms of ERα and AR in female and male mammals



Manolagas, S. C. *et al.* (2013) The role of estrogen and androgen receptors in bone health and disease
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2013.179

nature REVIEWS ENDOCRINOLOGY

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 111-118, 22 DEC 2011 DOI: 10.1002/jbmr.534
http://onlinelibrary.wiley.com/doi/10.1002/jbmr.534/full#fig1

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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

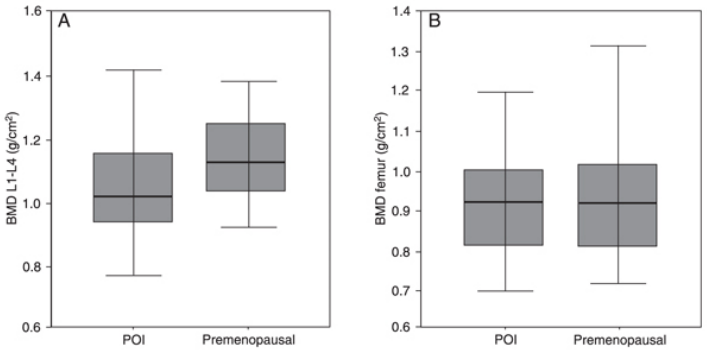

Figure 1. Bone mineral density (BMD) of the primary ovarian insufficiency (POI, N = 32) and premenopausal reference (N = 25) groups. *A*, L1-L4 lumbar bone mineral density (*P = 0.040; Student *t*-test). *B*, Femoral bone mineral density.

F. Amarante. Braz J Med Biol Res 2011; 44: 78-83.

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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

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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

Karlsson MK, et al Acta Orthop. 2005;76(1):2.

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 Notelovitz et al, J Bone Min Res 1991 Jun;6(6):583-90.
- 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).

Jackson et al, N Engl J Med. 2006;354(7):669

Premature menopause

- Estrogen therapy the mainstay of treatment
- HRT (not contraceptive)
- OCP

OXFORD UNIVERSITY PRESS

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

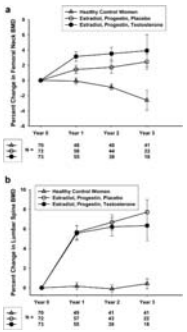
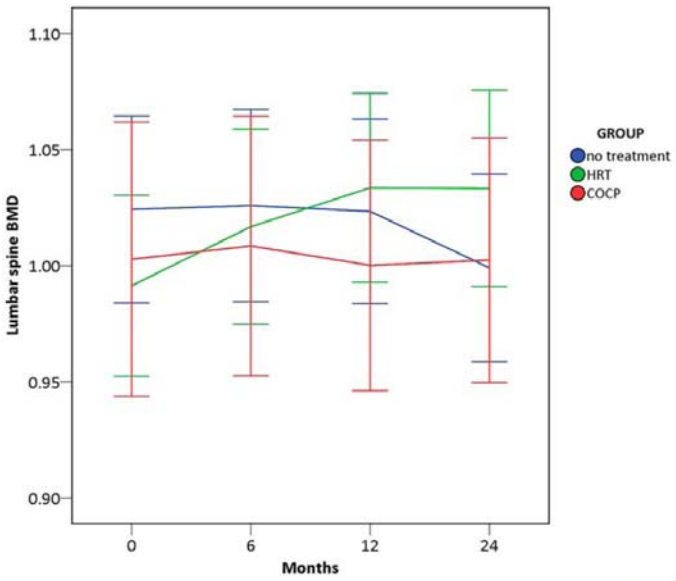
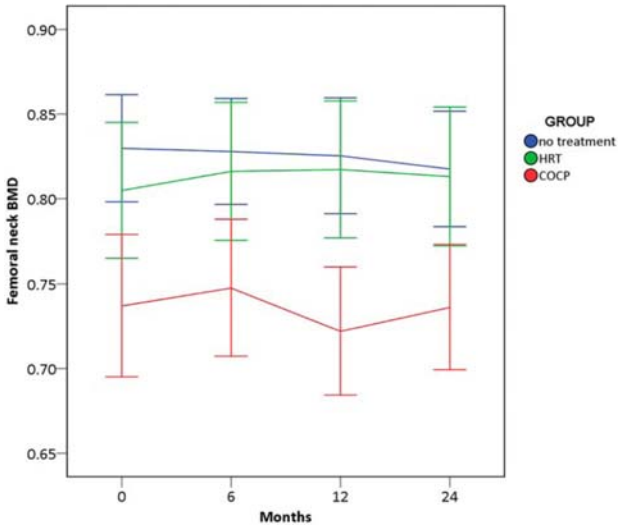


Figure Legend:
A, Mean (SEM) percentage change from screening in the femoral neck BMD. B, Mean (SEM) percentage change from screening in the lumbar spine BMD.

. 2014;99(9):3418-3426. doi:10.1210/jc.2013-4145



Cartwright et al, J Clin Endocrinol Metab, 2016, 101(9):3497–3505



Cartwright et al, J Clin Endocrinol Metab, 2016, 101(9):3497–3505

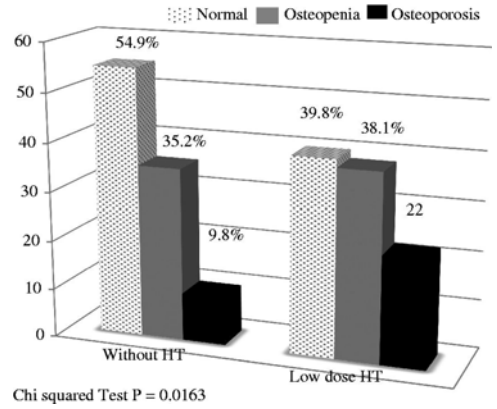


Figure 1. Percentage of women with POI without treatment (n = 107) or using standard dose HT (n = 132) with normal or compromised (osteopenia or osteoporosis) lumbar spine bone mineral density.

Published in: Helena Giraldo; Cristina Benetti-Pinto; Valeska Ferreira; Heraldo Garmes; Daniela Yela; Paulo Giraldo; *Gynecological Endocrinology* Ahead of Print
DOI: 10.1080/09513590.2016.1257602

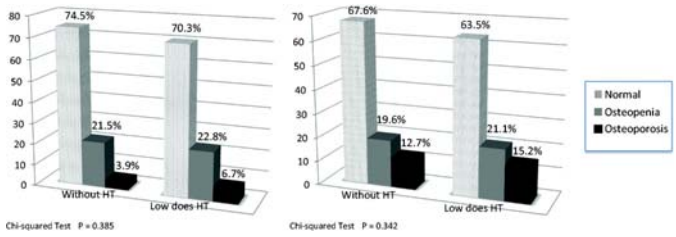


Figure 2. Percentage of women with POI without treatment (n = 107) or using standard dose HT (n = 132) with normal or compromised (osteopenia or osteoporosis) femoral neck and total femur bone mineral density.

Published in: Helena Giraldo; Cristina Benetti-Pinto; Valeska Ferreira; Heraldo Garmes; Daniela Yela; Paulo Giraldo; *Gynecological Endocrinology* Ahead of Print
DOI: 10.1080/09513590.2016.1257602

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

  Sestak et al, Lancet Oncol. 2014 Dec;15(13):1460-8.

- 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

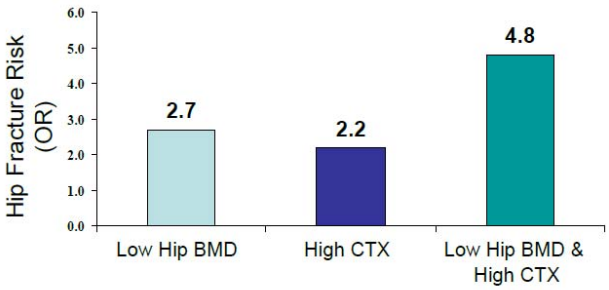
- Lots of guidelines but often difficult
- Fragility fracture
- Postmenopausal and T-score ≤-2.5
- FRAX 10 year risk of hip fracture ≥ 3%
- FRAX 10 year risk of any fracture ≥ 20%
- (antiresportives generally reduce fracture risk by 50% but treatment based on fracture risk assessment not evaluated in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

When whether to treat is not clear…

- ?use bone turnover markers to further clarify risk

BTMs Predict Fracture Independently of BMD

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



Garnero et al (1996) JBMR 11:1531-1538

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.

Antifracture efficacy of major interventions for postmenopausal osteoporosis

	Vertebral fracture risk		Non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis	Osteoporosis	Established osteoporosis
Alendronate	+	+	NA	+[hip]
Risedronate	+	+	NA	+[hip]
Ibandronate	NA	+	NA	+[1]
Zoledronic acid	+	+	NA	+
HRT	+	+	+	+[hip]
Raloxifene	+	+	NA	NA
Bazedoxifene	+	+	+	+[1]
Teriparatide/PTH	NA	+	NA	+[2]
Strontium ranelate	+	+	+[1, hip]	+[1, hip]
Denosumab	+	+	+[hip]	+

+ effective drug; [1] post-hoc analysis; [2] for teriparatide only, [hip] including hip fracture

JA Kanis, EV McCloskey, H Johansson, C Cooper, R Rizzoli, J-Y Reginster (2013) Osteoporosis Int 24: 23-57

esceo International Osteoporosis Foundation 25

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

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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

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