

Bone Health In Men
May 7, 2022

Robert A. Adler, MD
Central Virginia Veterans Affairs Health Care System
Virginia Commonwealth University
Richmond, Virginia, USA

1

Disclosures

- Site PI for Abaloparatide study in men (Radius Health)
- Will mention non-FDA approved treatment paradigms
- Opinions expressed are those of the speaker and not necessarily the U.S. Dept. of Veterans Affairs

2

Objectives

- Understand the differences in aging bone between women and men
- Appreciate the evaluation of men at risk for fracture
- Recognize new approaches to osteoporosis treatment in men

3

Men & Women: Hearts & Bones

- Women have CV events 10 yrs later than men – women do worse after events
- Men have bone events 10 yrs later than women – men do worse after events
- Information about heart disease based on studies in men
- Information about osteoporosis based on studies in women

4

Differences in Men & Women

- Bigger bones in men
- No menopause, rather a slow decrease in testosterone/estradiol with time
- Increased periosteal bone with aging in men compared to women
- Little attention paid to male osteoporosis
 - Reimbursement for DXA
 - TV ads osteoporosis: women only

5

Changes in Bone With Aging

- Males vs. Females
- Time of peak bone mass
- Loss of bone with time
- Differences in trabecular bone
- Differences in cortical bone

6

Aging in male & female bone

- In men, trabeculae thin with age
- In women, trabecular number decreases and spacing increases



7

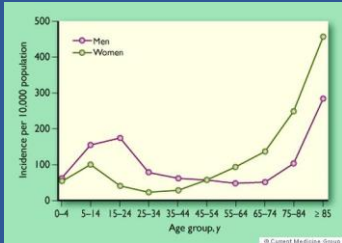
Cortical Bone & Aging

- With aging, vertebral strength decreases more in women
- With aging, men tend to retain the cortical portion on vertebrae better than women
- In long bones with aging, men tend to lay down more periosteal bone than women

BA Christiansen JIBMR 26:974, 2011

8

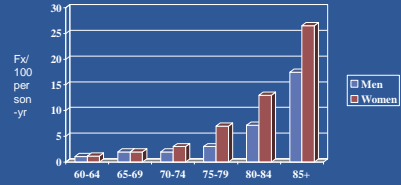
Incidence of Fractures in Men and Women



Donaldson LJ et al J Epidemiol Commun Health. 1990;44:241-245.

9

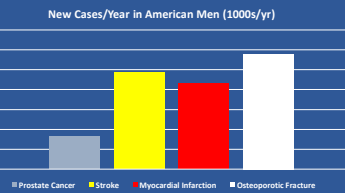
Age & Hip Fx: Rotterdam



Schuit et al Bone 34:195, 2004

10

Annual Incidence in American Men



11

Growing up Male

- Calcium and Vitamin D
- Exercise
- Computers
- Androgen Abuse
- Risky behavior

12

Male OP: Epidemiology

- About ¼ of all hip fractures are in men
- Men have about 2x death after hip fx
- < Age 50: more fractures in men (trauma)
- Spine fractures at middle age, hip later
- Life expectancy increasing faster in men
- More men are living long enough to fracture

R Burge J Bone Miner Res 22:465, 2007
E Bass Ann Epidemiol 17:514, 2007

13

Primary Osteoporosis: Type I

- Ages 51-75
- Women >> Men (6:1)
- Trabecular bone lost
- Vertebral and distal radius fractures
- Associated with menopause in women
- ?Cause in men

Riggs and Melton NEJM 314:1676, 1986

14

Type I OP in Men: Potential Causes

- **Increased urinary calcium excretion**
 - Long term negative calcium balance
 - Often have a history of kidney stones
- Decreased IGF-I with normal GH
- Low free estradiol
- ?Low free 25 (OH) Vitamin D
- ?Mastocytosis in marrow only
- **Cryptic secondary causes, especially hypogonadism**

CJ Rosen JCEM 83:2295, 1998
I Van Pottelbergh JCEM 89:4949, 2004

15

Primary Osteoporosis: Type II

- Age > 70
- Women > Men (2:1)
- Trabecular and Cortical Bone
- Hip and vertebral fractures
- Age-related, other factors

Riggs and Melton NEJM 314:1676, 1986

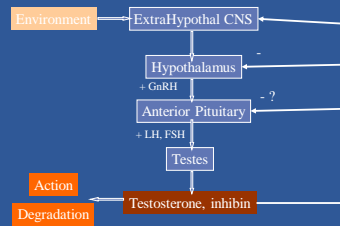
16

Causes of Secondary OP

- Hypogonadism
 - Primary and secondary (organic)
 - Cancer chemotherapy (cyclophosphamide)
 - **Androgen deprivation for prostate cancer**
 - **?Testosterone decline with aging**
- Chronic disease
- Medications: examples
 - Anti-seizure meds → OP & osteomalacia
 - Neuroleptics (↑ Prolactin), PPIs, TZDs,
 - Anti-depressants?

17

Hypothalamic-Pituitary-Testicular Axis



18

PRIMARY HYPOGONADISM- CAUSES

- Klinefelter's syndrome (1/500 Male Births)
- Mumps and other orchitis
- Trauma or radiation to testes
- Cancer chemotherapy

19

Secondary Hypogonadism: Causes

- Pituitary or hypothalamic tumors
- Surgery or radiation of pituitary or hypothalamus
- **Traumatic Brain Injury**
- Hemochromatosis
- Hyperprolactinemia
- Kallman's Syndrome (↓ GnRH)
- **Obesity/Diabetes/Metabolic Syndrome**

20

Hypogonadism: Mixed Causes

- Severe illness/malnutrition
- Alcohol excess
- Glucocorticoid excess (Rx or Cushing's)
- HIV/AIDS
- Medications

21

Hypogonadism: Medications

- Glucocorticoids
- Ketoconazole
- Spironolactone
- Androgen receptor blockers (eg, Nilutamide)
- Histamine 2 Blockers? PPIs?
- Check Point Inhibitors
- Cyclophosphamide
- GnRH analogs, Abiraterone

22

Declining Testosterone in Aging

- Common but mild decrease
- In parallel with ↓bone density & muscle
- Better correlation of E_2 & BMD
- Different from organic causes of hypogonadism
- Lower T probably not a major cause of bone loss in most older men, but a risk

S. Khosla, JCEM 83:2266, 1998

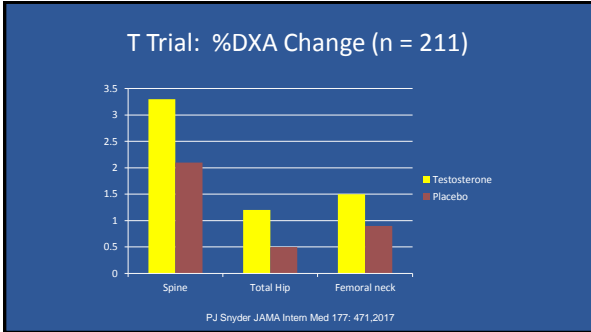
23

Total T: Lowest 2.5%ile

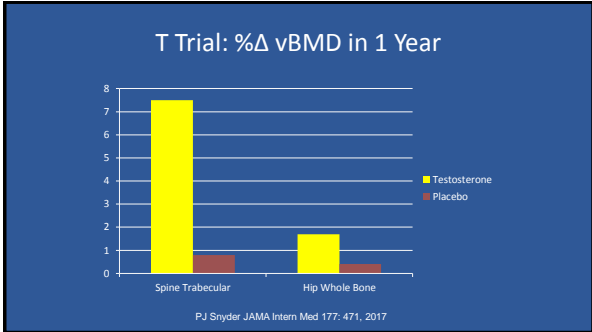
	19-39	40-49	50-59	60-69	70-79	80-99
Non-obese	267	235	219	218	218	157
All Men	229	208	192	190	190	119

TG Travison, J Clin Endocrinol Metab 102:1161, 2017

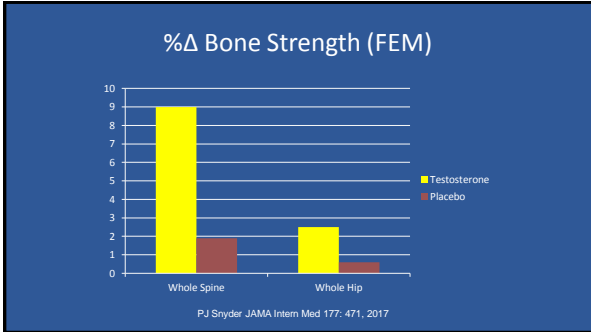
24



25



26



27

- ### Hypogonadism & OP
- Organic hypogonadism causes OP
 - Testosterone replacement increases bmd
 - T indicated for younger men
 - Older men: T Rx has potential side effects!
 - No Fracture Reduction Data!
 - Endocrine Society: Use osteoporosis specific drug to prevent fracture
- NB Watts JCEM 97:1802, 2012

28

OP in men: Etiology Summary

- Idiopathic OP in middle aged men: Spine
- Aging-associated OP: ↑ “old old” : Hip
- Secondary causes important in men
- Testosterone for organic hypogonadism
- ?T for men with the mildly ↓ T of aging?
- Most older men with osteoporosis have normal testosterone level for age – Rx with osteoporosis-specific medication

29

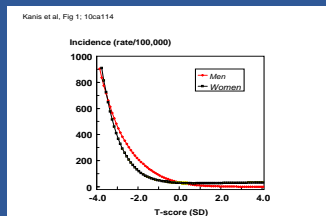
DIAGNOSIS: DXA and Risk Calculation

- At age 50: Lifetime Fracture Risk is 13-25%
- NBHA: OP = T-score ≤ -2.5 ■ FRAX $\geq 3\%$ / $\geq 20\%$
- T-score ≤ -2.5 in NHANES 2005-2008:
 - Men ≥ 50 years old: 4%
 - Men ≥ 80 years old: 9.2%
- ↑Fx risk by FRAX in NHANES 2005-2008:
 - Men ≥ 50 years old: 13.4%
 - Men ≥ 80 years old: 37.8%

ES Siris, Osteoporos Int 25:1439, 2014
NC Wright Osteoporos Int 28:1225, 2017

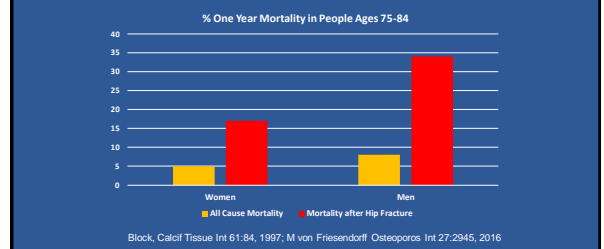
30

Fracture Risk Vs. Hip T-score



31

One Year Mortality After Hip Fracture



32

Post-Hip Fracture

- High one year mortality!
- High incidence of a second fracture!
- 50% of survivors never regain previous status of independence!!!!

33

No Attention to Male Osteoporosis

- Not enough studies in men
- Guidelines/articles target women
- Lack of reimbursement for DXA in men
- Competing medical problems
- OP is asymptomatic until fracture
- "I just fell, doc"

34

Management Strategies/Topics

- Diagnosis
 - Screening, use of DXA
 - Other testing
- Treatment
 - Current approach
 - Time for a new paradigm?
- Long Term Management

35

DXA Testing in Men

- What age? Which men?
- ACPM, NOF, ISCD, Endocrine Society: DXA at 70, earlier with risk factors
- USPSTF: Not enough data
- VA: Case finding of higher risk older men
- Targeted screening works

Hochberg & Adler, Nature Clin Prac Rheum 4:626, 2008,
RA Adler, Fed Practitioner 29:31, 2012

36

Risk Factors in U.S. Veterans

- Low trauma fracture after age 45
- X-ray evidence of osteopenia or fracture
- ADT, prednisone, hypogonadism
- Anti-convulsant Rx for > 2 years
- Bariatric/gastric surgery, malabsorption
- Excess alcohol
- Current smoking

RA Adler, Federal Practitioner 29:33, 2012

37

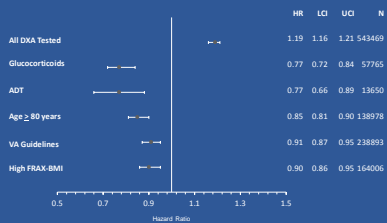
Testing for OP with DXA

- Does screening work in men?
- Veterans Affairs Study – entire VA database
 - General DXA Testing ineffective
 - Targeted Testing leads to fewer fractures
 - Age \geq 80
 - ADT or Prednisone
 - High risk by FRAX (using BMI)
 - Age \geq 65 + VA Risk Factor

© Colon-Emeric Mayo Clin Proc 93:1749, 2018

38

Screening Male Veterans For Osteoporosis by DXA



CS Colon-Emeric, Mayo Clin Proc 93:1749, 2018

39

Screening with DXA: Conclusions

- Targeted DXA testing
- Young white female database is now used for calculating T-score for everybody
- Reimbursement for DXA testing in men remains challenging in U.S. Elsewhere?

40

Evaluation other than DXA

- History and physical exam
- Modest laboratory evaluation
 - Serum Ca, PO_4 , Alb, eGFR, alkaline phosphatase
 - 25-OH Vitamin D. When normal PTH
 - 24-hour urine calcium (when D normal)
 - CBC, occasional SPEP, UPEP
 - Sometimes: TSH, Testosterone (\pm LH, FSH, prolactin), celiac antibodies

RA Adler, Best Pract Res Clin Endocrinol Metab 32:759, 2018

41

Younger Men with Osteoporosis

- Present with vertebral fractures (40's, 50's)
- Secondary osteoporosis
 - Glucocorticoids and other medications
 - Hypogonadism
 - Hypercalciuria
 - Celiac disease
 - Idiopathic

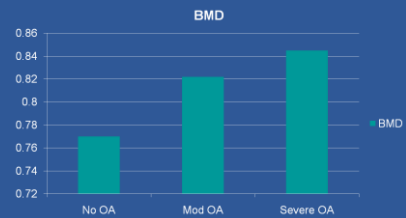
42

FRAX: Validated Risk Factors

- BMD of femoral neck
- BMI (can substitute for BMD)
- Age
- Prior Fragility Fracture
- Glucocorticoid Exposure
- Parental history of Hip Fracture
- Current Smoking
- Excess Alcohol Intake
- Secondary Causes (e.g. Rheumatoid Arthritis)
- www.shef.ac.uk/FRAX/
- www.fractureriskcalculator.com

43

Femoral Neck \pm OA



RK Chaganti, Osteoporos Int 21:1307, 2010

44

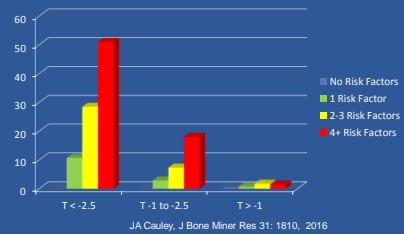
FRAX for Men: Pros & Cons

- DXA + Risk Factors
- Fem Neck has highest gradient of risk
- Large populations used to construct FRAX
- Available on DXA
- Other risks: Falls, DM
- Severity of Fx history
- Severity of RA
- Dose of glucocorticoid
- Age of parental hip fx
- Doesn't use spine
- OA effect on Fem Neck

S Balm, Curr Osteoporos Rep 10:28, 2012
S Yang, J Bone Miner Res 31:1753, 2016

45

Hip Fx Risk in Older Men (MrOS): Femoral Neck T-score + Risk Factors



46

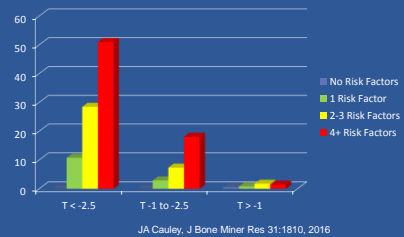
Hip Fracture Risk Factors in Older Men (MrOS Study)

- Age \geq 75
- Less protein in diet
- Any fracture after age 50
- Divorce!
- Tricyclic anti-depressants
- Hypoglycemic agents
- Height loss
- Hyperthyroidism
- Parkinson's Disease
- Can't do chair stands
- \downarrow Executive Function
- Current Smoking

JA Cauley, J Bone Miner Res 31:1810, 2016

47

Hip Fractures/1000 Patient-Years: Femoral Neck T-score + Risk Factors



48

Diagnosis Summary

- Identify high risk men
- History & PE for secondary causes/risk factors
- DXA still the best predictor of fracture
- Calculate FRAX with Femoral Neck BMD
- Limited lab tests
 - CBC, Chemistries, TSH
 - 25 (OH) vitamin D levels; when normal PTH
 - Urinary calcium excretion
 - T/LH/FSH/SPEP/UPEP/Celiac, etc.
- Find underlying disorders requiring specific treatment

RA Adler, Best Pract Res Clin Endocrinol Metab 32:759, 2018

49

FDA Approved Rx for Men

- Alendronate, Risedronate → ↑ BMD in men
- Zoledronic Acid → ↑ BMD in men
- Denosumab → ↑ BMD in men
- Teriparatide → ↑ BMD in men
- Some morphometric fracture reduction
- Most Rx studies: $T \leq -2.5$ by the male database or $T \leq -2$ plus a fragility fracture
- Testosterone not approved for OP but...

50

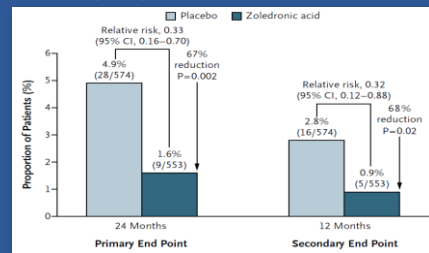
Study with 1^o Fracture Outcome

- Using male database:
 - $T < -2.5$ OR
 - $T < -1.5$ + osteoporotic fracture
- 2 year study: ZA vs. placebo

S Boonen, NEJM 367:1714, 2012

51

Morph Spine Fx After ZA in Men



S. Boonen, NEJM 367:1714, 2012

52

Side Effects of BPs & Denosumab

- GERD with orals bisphosphonates
- Acute Phase Reaction with IV
- Esophageal CA (oral), Atrial Fib (IV)
- Inflammatory Eye Disease (rare)
- Osteonecrosis of the Jaw (ONJ)
- Atypical Femoral Fractures (AFF)

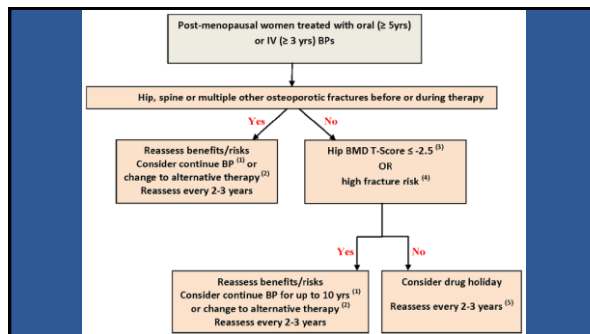
53

Long Term Management

- There are NO long-term studies in men
- Management based on studies in studies in women

RA Adler, J Bone Miner Res 31:16, 2016

54



55

Bisphosphonate Rx-Adler Modification

- 5 years of bisphosphonates for moderate-high fracture risk
 - 5 years of oral bisphosphonate
 - i.v. zoledronic acid q 18-20+ months = 5 years of Rx
- At 2-3 and at 5 years, assess fracture risk again
 - DXA (T < -2.5), history of fracture
 - Side effects – risks predictable?
 - Other factors
 - Meds (e.g. ± glucocorticoids, aromatase inhibitor, ADT)
 - Falling and frailty
 - Competing causes of mortality
- Assess again periodically (q2-3 years forever!)

RA Adler J Bone Miner Res 31:16, 2016; RA Adler Endocrine 51: 222, 2016
J Ward Osteoporos Int 27:2681, 2016; A Gustafsson Bone 68:125, 2016

56

Alternatives to Bisphosphonates

- Denosumab
 - Potent anti-resorptive
 - Useful in CKD
- Teriparatide
 - Only anabolic FDA approved for men
- Abaloparatide
- Romosozumab
- Testosterone for those with hypogonadism

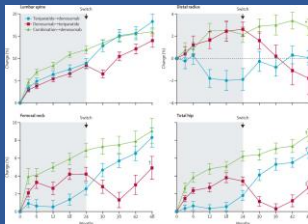
57

New Paradigm?

- How would you treat the high-risk patient if:
 - All osteoporosis meds cost the same as generic oral alendronate?
 - Could be prescribed without jumping through hoops?
 - Patient care was based on what is best for the patient?

58

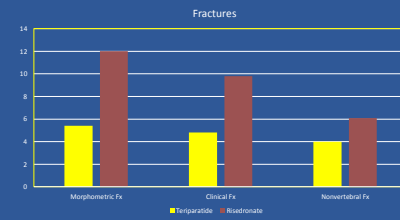
DATA-SWITCH Study (Women)



BZ Leder, Lancet 386:1147, 2015

59

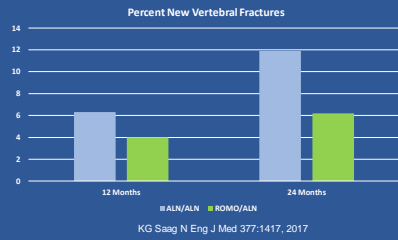
VERO Trial (Women): 2 Years Teriparatide vs. Risedronate



DL Kendler, Lancet doi 10.1016/S0140-6736(17)32137-2

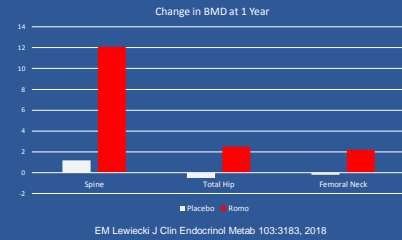
60

New Vert Fx: Romo Vs. ALN (Women)



61

Romozosumab in Men



62

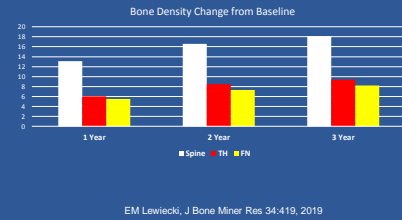
Newer Treatment Paradigms

- Use of anabolics first?
 - Consider in the very high-risk category
 - Will this alter incidence of ONJ or AFF?
 - Can use teriparatide for > 2 years now
- Use denosumab for 2 years first or after anabolics?
- Can aggressive Rx improve BMD enough to stop Rx?

Leder BZ JBMR Plus 2:62, 2018
 Cozman F J Bone Miner Res 35:220, 2020
 JA Kanis, Osteoporos Int 31:1, 2020

63

Romozosumab, then 2 Years of Denosumab in Women



64

New Paradigm: Romo/Dmab/ZA?

- Romo (1 year), Denosumab (2 years), ZA X 1
- Would this be enough to sharply lower fracture risk?
- Could patients then be given a long drug holiday?
- Would this lower risk of AFF, ONJ?
- What to do after the drug holiday?
- How to study this regimen?

F Cosman, JBMR Plus 5:e10546, 2021

65

Practical Approach 2022 & Beyond: All Patients

- A Comprehensive Approach
- Fall Risk Reduction
- Adequate Calcium/Vitamin D/Protein
- Weight Bearing Exercise
- Tailor to the Patient
- Virtual/Phone Visits?
- Make osteoporosis in men a priority

66

Borderline Fracture Risk

- Try to Avoid Bisphosphonates or Other Rx
- Conservative Treatment
 - Emphasize diet, exercise, fall risk reduction
- Repeat DXA at 2-3 Years
- Use FRAX to Demonstrate Low Fracture Risk

67

OP by DXA, Osteopenia + Fx, High FRAX

- Alendronate or Zoledronic Acid
 - Consider ZA q 18 months (3 Infusions/5 years)
- Clinical Assessment Annually; DXA at 2-3 and 5 years
 - Some experts use BTMs to assess adherence/response
- Major Reassessment at 5 years
- Reassess q 2 Years thereafter
- Continue or Change Rx if Fracture Risk Remains High

68

Very High Fracture Risk

- Consider Anabolic Treatment First
 - Teriparatide 2+ years, Abaloparatide 1.5 to 2 years
 - Romosozumab for 1 year
 - Then anti-resorptive Rx
- Educate about Long Term Benefits and Risks
- Compare Fracture Risk by FRAX and Risk of Side Effects
- Manage Longitudinally Similarly, but consider aggressive Rx
 - Annual Clinical Assessment
 - DXA q 2-3 years
 - Comprehensive Approach

EM Lewiecki J Clin Endocrinol Metab 103:3183, 2018

69

But How to Get Osteoporosis on the Radar for Men?

- **This is the biggest challenge**
- Changing clinician and patient behavior!
- Osteoporosis is silent – until there is a fracture
- Medications don't make patients feel better
- Focus on the highest risk patients:
 - Already fractured
 - Medications that increase fracture risk
 - Glucocorticoids, ADT, Anti-Seizure Meds

70

Thank you for your attention

71