33 Y Female with back pain

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Dr. Upala does not have any relevant financial relationships with any commercial interests

Learning Objectives

- Understand the causes of low BMD and fractures in premenopausal women
- Understand the principles of management of osteoporosis in premenopausal women with secondary osteoporosis and idiopathic osteoporosis

HPI

- 33 Yrs female with a past medical history of non-CF bronchiectasis s/p bilateral lungs transplantation in 2015, vitamin A and zinc deficiency, GERD, malnutrition who is **referred for back pain**

HPI

- Diagnosed with low bone mass in 2010 presented with bone pain and had DEXA scan which revealed low BMD (no data)
- Denies family hx of fracture or osteoporosis
- 2010-2011, treated with Fosamax 70 mg once weekly, stopped because of stable bone density

HPI

- Denies previous falls or fractures
- Patient reports young adult height of 4’11; Current height: 4'11
- Ca supplements: 648 mg bid, no dairy product, MTV 1 tab qd
- Mild sun exposure throughout life
- No exercise
- Had kidney stone in 2012, denies family history of kidney stones
- Menarche at age 14-15 with regular periods, no OCP, no pregnancy, not sexually active
- Weight: 5 kg weight gain after lung transplant
- + corticosteroids, immunosuppressant, proton pump inhibitors

Past Medical History

- Bronchiectasis
  - Non-CF bronchiectasis. Negative sweat test and no CFTR found
- Chronic respiratory failure
- GERD
- GI bleed
- Malnutrition (was on TPN and G-tube in 2015)
- Low bone mass
- Intestinal malabsorption (vitamin A and Zinc deficiency)
- Depression

Past Surgical History

- Bilateral lungs transplant in 06/25/2015
- Thoracotomy

Allergy

- Vancomycin

Social History

- Lives with family
- Unemployed
- No exercise
- No Tobacco/Second-hand
- No EtOH
- No illicits

Medication prior visit

- Biotin 1 tab daily
- Calcium carbonate 648 mg 1 tab twice daily
- Esomeprazole 40 mg 1 tab daily
- Mirtazapine 30 mg 1 tab daily
- MTV/Iron/D3 1 tab daily
- Mycophenolate mofetil 500 mg 1 tab twice daily
- Olanzapine 5 mg 1 tab daily
- Prednisone 5 mg 1 tab daily
- Sulfamethoxazole-trimethoprim-SS 400-80 mg 1 tab every Monday, Wednesday and Friday
- Tacrolimus 0.5 mg 1.5 tab every 12 hours

ROS

- Constitutional: No fevers, night sweats, fatigue, appetite change
- HEENT: No photophobia, blurred vision, pain, hearing loss, sinus congestion, sore throat, mouth sores, difficulty swallowing, thirst, hoarseness, facial plethora, exophthalmos
- Resp: No cough, dyspnea, increased WOB
- CV: No CP, DOE, orthopnea, PND, palpitations, LE edema, claudication, HTN
- GI: No abdominal pain, nausea, vomiting, diarrhea, constipation, hematochezia, melena
- GU: No dysuria, urgency, polyuria, hematuria, flank pain
- MSK: **+myalgias, joint pain, back pain**
- Neuro: No syncope, seizures, weakness, numbness, paresthesias, headaches, tremors, memory problems
- Heme: No adenopathy or easy bruising/bleeding, hx of blood clots
- Endo: No heat or cold intolerance, dry or oily skin, dry hair, hair loss, glucose intolerance
- Derm: No rashes, ulcers, abdominal striae, hirsutism, acne, hyper or hypopigmentation
- Psych: No mood changes, sleep disturbance, anxiety, audio/visual hallucinations

Physical Exam

- Vital Signs: BP 96/80 | Pulse 98 | Ht 149.9 cm (4' 11") | Wt 47.4 kg (104 lb 8 oz) | BMI 21.11 kg/m2
- Gen: Well-developed and well-nourished. No distress. Appear stated age.
- HEENT: Conjunctivae clear, sclerae anicteric. Nares without discharge. O/p moist
- Neck: Supple, normal range of motion, no thyromegaly or nodules.
- CV: RRR, no murmurs, ext warm, no edema.
- Pulm/Chest: Clear bilaterally, no rales, rhonchi or wheezes. Effort normal.
- Abd/GI: BS+, soft, nt, nd, no guarding.
- **MSK: Normal tone/bulk. No scoliosis or kyphosis. No tenderness to palpation over spine or paraspinous muscles. Normal neck ROM and posture. No proximal muscle weakness. No joint effusions.**
- Neuro: AOx3, EOMI. No facial asymmetry. Strength 5/5 symmetric in upper and lower extremities. Normal gait.
- Skin: Skin is warm, dry no rashes.
- Psychiatric: Normal mood and affect, appropriate.

Lab

- Calcium: 9.4
- Actual Ca++: 4.64
- Inorganic Phosphate: 2.7
- Bone specific ALK: 13 (<14)
- PTH, Intact: 59
- C-Telopeptide: 304 (93-630)
- Vitamin D, 25-OH: 28
- Glucose: 77
- BUN: 8
- Creatinine: 0.6
- Albumin: 4.3
- Bilirubin, Total: 0.3
- AST: 20
- ALT: 14
- Hb A1C: 4.5

Urine

Urine Creatinine, Random: 38

24 urine

Volume: 1275

Urine Creatinine, Timed: 485 (L)

Creatinine Clearance: 48 (L)

Urine Calcium, Timed: 64 (L)

Imaging

- CXR: status post bilateral lung transplant, unremarkable in appearance

DEXA scan

BMD	7/19/12	9/17/14	1/2/16	10/12/17
Spine BMD	0.795	0.880	0.830	0.827
Spine Z score	-3.2	-1.7	-2.1	-2.4
% changes		+10.7%	-5.7%	Stable
Femoral BMD	0.755	0.739	0.691	0.722
Femoral Z score	-2.4	-1.5	-1.8	-1.7
% changes		Stable	Stable	+5.7%

lungs transplant in 06/25/2015

5 kg weight gain

ISCD Nomenclature

BMD Reporting in Females Prior to Menopause and in Males Younger Than Age 50

- No "osteopenia“ in men under 50 and women who are premenopausal
- Z-scores, not T-scores, are preferred. This is particularly important in children
- A Z-score of -2.0 or lower is defined as “below the expected range for age”, and a Z-score above -2.0 is “within the expected range for age”

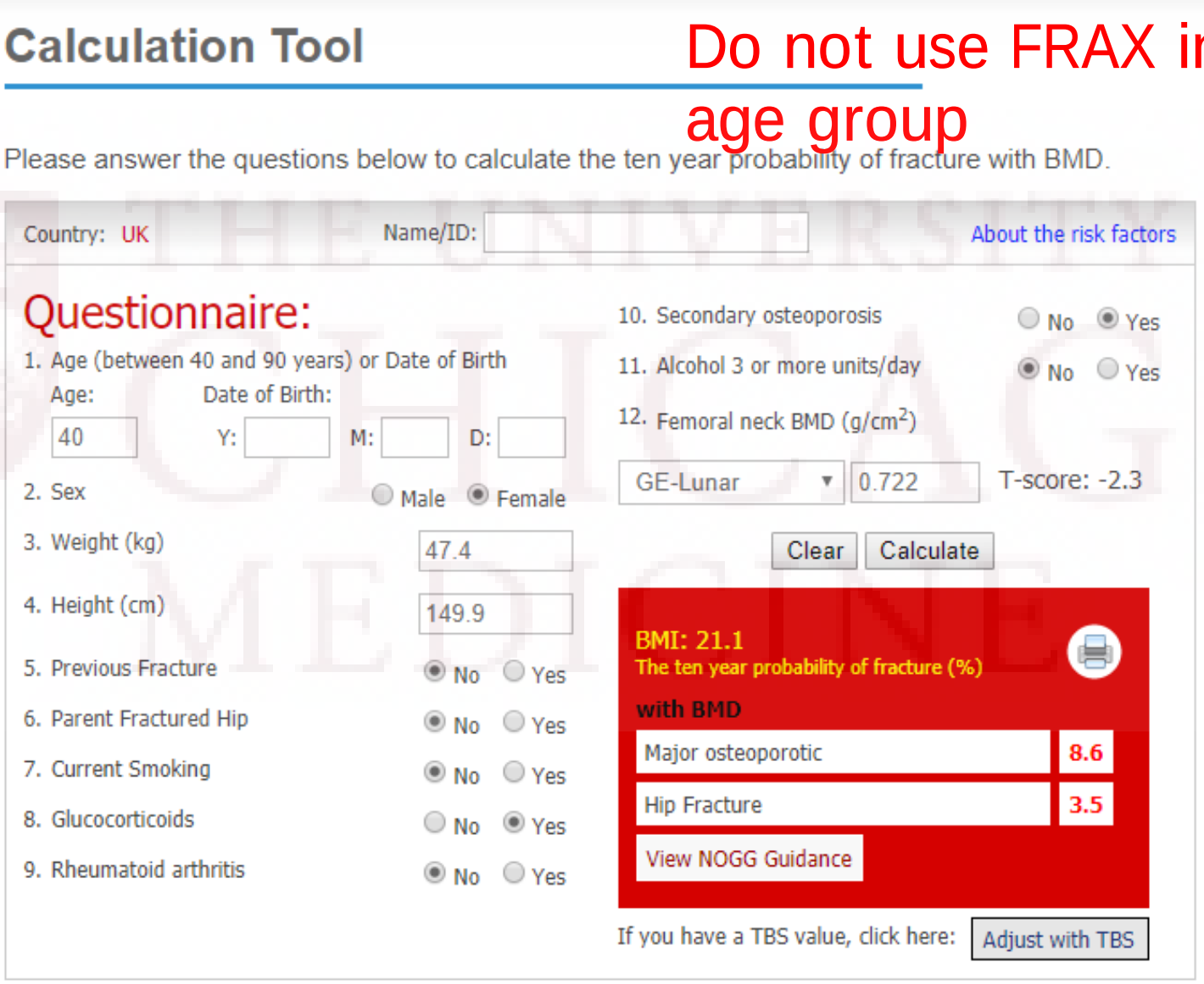
2015 ISCD Official Positions

Vertebral Fracture Assessment

10/12/17

- VFA was visualized from T4 to L4 and showed no fractures

FRAX


Calculation Tool
Do not use FRAX in her age group
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: UK
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
Age:
Date of Birth:
40
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
47.4
4. Height (cm)
149.9
5. Previous Fracture
No
Yes
6. Parent Fractured Hip
No
Yes
7. Current Smoking
No
Yes
8. Glucocorticoids
No
Yes
9. Rheumatoid arthritis
No
Yes
10. Secondary osteoporosis
No
Yes
11. Alcohol 3 or more units/day
No
Yes
12. Femoral neck BMD (g/cm2)
GE-Lunar
0.722
T-score: -2.3
Clear
Calculate
BMI: 21.1
The ten year probability of fracture (%)
with BMD
Major osteoporotic
8.6
Hip Fracture
3.5
View NOGG Guidance
If you have a TBS value, click here:
Adjust with TBS

Clinical question

- What to do in premenopausal low bone mass?
- Should we treat or monitor for now?

Common Secondary Causes of Low Bone Mass in Premenopausal Women

Cause
Anorexia nervosa
GI malabsorption (eg. celiac disease, postoperative states)
Vitamin D and/or calcium deficiency
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Hypogonadism
Hypercalciuria
Rheumatoid arthritis and other inflammatory conditions
Alcoholism
Renal disease
Liver disease
Osteogenesis imperfecta
Marfan's syndrome
Homocystinuria

Medications
Glucocorticoids
Immunosuppressants (cyclosporine)
Antiseizure medications (particularly phenobarbital and phenytoin)
GnRH agonists (when used to suppress ovulation)
Heparin
Cancer chemotherapy
SSRIs
Depot medroxyprogesterone acetate
Excess thyroid hormone

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.

Glucocorticoid-induced osteoporosis (GIOP)

- The most common cause of secondary osteoporosis
- The underlying pathology with GIOP: reduced bone formation rather than excessive bone resorption
- Various guidelines exist for the diagnosis and treatment of GIOP
- In patients in whom taking glucocorticoids puts them at moderate to high risk of fracture treatment is normally recommended. This would be with either a bisphosphonate or teriparatide

Glucocorticoid-induced osteoporosis (GIOP)

- American College of Rheumatology (ACR) guidelines recommend intervention based upon risk of fracture, guided by FRAX
- For adults ≥40 years
  - Low risk – 10-year risk of hip or a major osteoporotic fracture of ≤1 and <10 %
  - Medium risk – 10-year risk of hip or a major osteoporotic fracture >1 to <3 % and 10 to 19 %
  - High risk – History of a fragility fracture, a lumbar spine or hip T-score below -2.5, or 10-year risk of hip or a major osteoporotic fracture ≥3 and 20 %

  For adults <40 years
  - Low risk – No medium or high risk factors other than glucocorticoid treatment
  - Medium risk – Hip or spine Z-score <-3, or rapid bone loss (≥10 %over one year) and continuing prednisone ≥7.5 mg/day for ≥6 months
  - High risk – History of a fragility fracture
- Recommend oral bisphosphonates for adults at medium or high risk of major fracture, considered teriparatide, denosumab, and raloxifene
- Yearly BMD

Glucocorticoid-induced osteoporosis (GIOP)

- The National Osteoporosis Guideline Group in the UK recommends using FRAX (adjusted for glucocorticoid dose) and antiresorptive therapy should be initiated in patients at highest risk for fracture (≥70 years of age, history of prior fragility fracture, or taking large doses of glucocorticoids [≥7.5 mg prednisolone/day])
- The International Osteoporosis Foundation and the European Calcified Tissue Society recommend therapy in postmenopausal women and men who are ≥70 years, have a previous fragility fracture, or a dose of prednisolone ≥7.5 mg daily for ≥3 months

Low Bone Mass after Transplantation

- **Study:** Observational study
- **Population:** Taiwan's National Health Insurance Research Database, 9428 recipients of SOT and 38,140 sex- and age- matched control between 1997 and 2010 to compare the incidence and risk of bone disorders
- **Results:** Hazard ratio (HR) of osteoporosis after SOT: 5.14 (95% CI, 3.13-8.43), and the HR of related fractures: 5.76 (95% CI, 3.80-8.74)
- The highest HRs were observed in male patients and in those aged 50 years or younger

Yu T, Mayo Clin Proc. 2014

Low Bone Mass after Transplantation

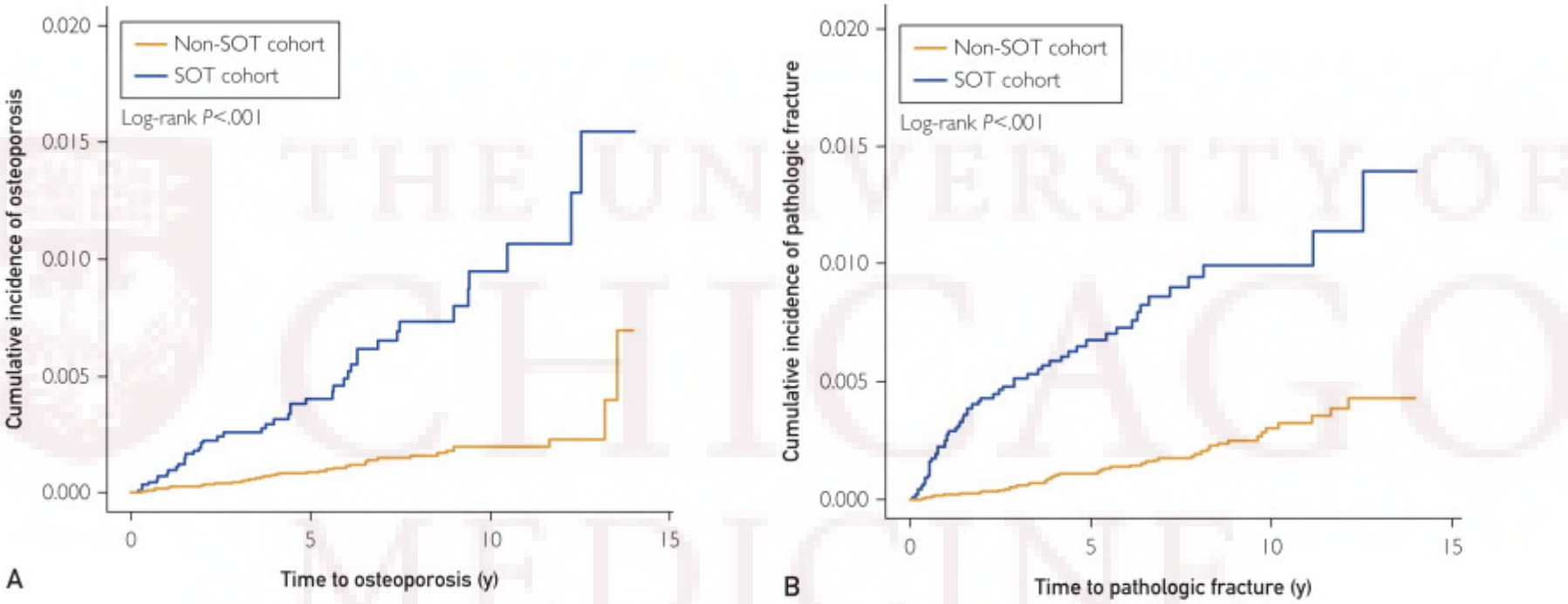


Figure Cummulative incidences of osteoporosis (A) and pathologic fracture (B) in the solid organ transplantation (SOT) and non-SOT cohorts using the Kaplan-Meier method

Yu T, Mayo Clin Proc. 2014

Low Bone Mass after Transplantation

Results

Variable	Events (No.)	Person-years	Rate [b]	Crude (relative) HR (95% CI)	Adjusted HR (95% CI) [c]
Osteoporosis	41	207,632	1.97		
Non-SOT				1 [Reference]	1 [Reference]
Kidney recipients	24	32,849	7.31	3.66 (2.21-6.06) [d]	3.40 (1.78-6.48) [d]
Liver recipients	8	8968	8.92	4.74 (2.21-10.2) [d]	4.40 (1.97-9.82) [d]
Heart recipients	8	3746	21.4	10.5 (4.93-22.5) [d]	8.40 (3.71-19.0) [d]
Lung recipients	2	154	129.9	70.7 (16.9-296.1) [d]	191.4 (41.6-881.4) [d]
Pathologic fracture					
Non-SOT	55	207,651	2.65	1 [Reference]	1 [Reference]
Kidney recipients	25	32,882	7.60	2.85 (1.78-4.57) [d]	3.42 (1.89-6.17) [d]
Liver recipients	25	8940	28.0	10.7 (6.65-17.4) [d]	9.68 (5.78-16.2) [d]
Heart recipients	5	3752	13.3	5.08 (2.03-12.7) [d]	3.46 (1.31-9.12) [e]
Lung recipients	3	154	194.8	81.2 (25.1-262.5) [d]	326.6 (92.2-1156.9) [d]

a HR = hazard ratio; SOT = solid organ transplantation.

Yu T, Mayo Clin Proc. 2014

Idiopathic Osteoporosis in Premenopausal Women (IOP)

- Premenopausal women with no identifiable etiology after extensive evaluation for secondary causes
- IOP primarily affects Caucasians, men and women equally
- Fractures may be multiple, occurring over a 5-10 years period
- May present with acute vertebral compression fractures during pregnancy or lactation
- Mean age at diagnosis: mid thirties
- Abnormalities of osteoblast function and decreased IGF-I have been found in most studies of men with IOP

Guidelines for BMD Testing in Premenopausal Women

History of fragility fracture
Diseases or conditions associated with low bone mass or bone loss
Premenopausal estrogen deficiency (eg, hyperprolactinemia, athletic triad, prolonged amenorrhea)
Eating disorders
Chronic obstructive pulmonary disease
Cystic fibrosis
Hyperparathyroidism
Rheumatoid arthritis
Inflammatory bowel disease
Celiac disease
Medications that cause bone loss
Glucocorticoids
Depot progesterone
GnRH agonists
Aromatase inhibitors
Antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproate)
If pharmacologic therapy of osteoporosis is being considered
Being monitored for effectiveness of pharmacologic therapy for osteoporosis

Management

- No official guidelines for management of premenopausal women with low bone mass
- All recommendations are based upon expert opinion
- Lifestyle modifications should be encouraged for all women with low bone mass given that peak bone mass may improve into the fourth decade
- The following should be encouraged:
  - Adequate calcium intake (1000–1200 mg daily), preferably from dietary sources
  - Adequate vitamin D intake (400-800 IU vitamin D3 daily) or sufficient to maintain serum 25-OHD levels above 20-30 ng/mL
  - Regular physical activity, particularly weight-bearing exercise
  - Cessation of smoking
  - Avoidance of excessive dieting
  - Maintenance of normal body weight
  - Avoidance of excess alcohol, caffeine and phosphorus containing drinks

Management

- **Study:** Retrospective study
- **Population:** 16 premenopausal women with IOP (aged 35.7+/-7 years), mean follow-up: 3 years
- BMD at the lumbar spine and femoral at baseline and yearly
- Rx: calcium and vitamin D, advised to increase physical activity

Peris P, Clic Rheumatol. 2007

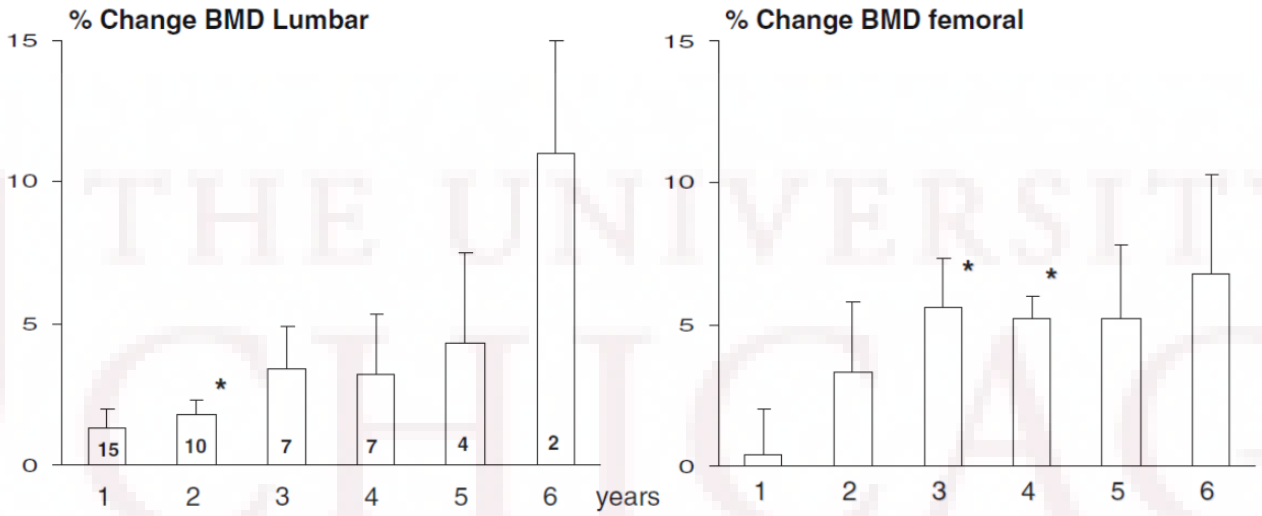


Fig. 1 Percentage of change of lumbar and femoral neck BMD throughout the study expressed by years of follow-up (mean± SD). The numbers included in the *bars* indicate the number of patients at this time. **P*<0.05 vs baseline values

A significant increase in BMD (1.9% mean increase in lumbar spine, p= 0.021, at 2 years and 5.6% mean increase in femur, p=0.04, at 3 years)
No new skeletal fractures during the follow-up

Peris P, Clic Rheumatol. 2007

Management

- Rx secondary cause of osteoporosis
  - Institution of a gluten-free diet in celiac disease
  - Parathyroidectomy in patients with primary hyperparathyroidism
  - Discontinuation of medroxyprogesterone acetate
  - Oral contraceptives for women with oligo- or amenorrhea

Management

- Pharmacologic therapy should be avoided unless the patient is losing bone or fracturing
- Summarized effects of medication in premenopausal women with osteoporosis
  - Selective estrogen receptor modulators (SERMs) such as raloxifene should not be used
  - Bisphosphonates carry a category C rating for safety in pregnancy as they cross the placenta and accumulate in fetal bones in an experimental rat model. Although they are probably safe, their long half-life in bone makes their use in reproductive-age women a concern. In premenopausal women without fractures or known secondary causes for fractures, bisphosphonates are generally not indicated

Management

- Teriparatide has been shown to prevent bone loss in premenopausal women on GnRH agonists for endometriosis, to increase BMD in premenopausal women with glucocorticoid-induced osteoporosis, and with IOP, and with pregnancy- and lactation-associated osteoporosis

Choe EY, JBMR.2012

Management

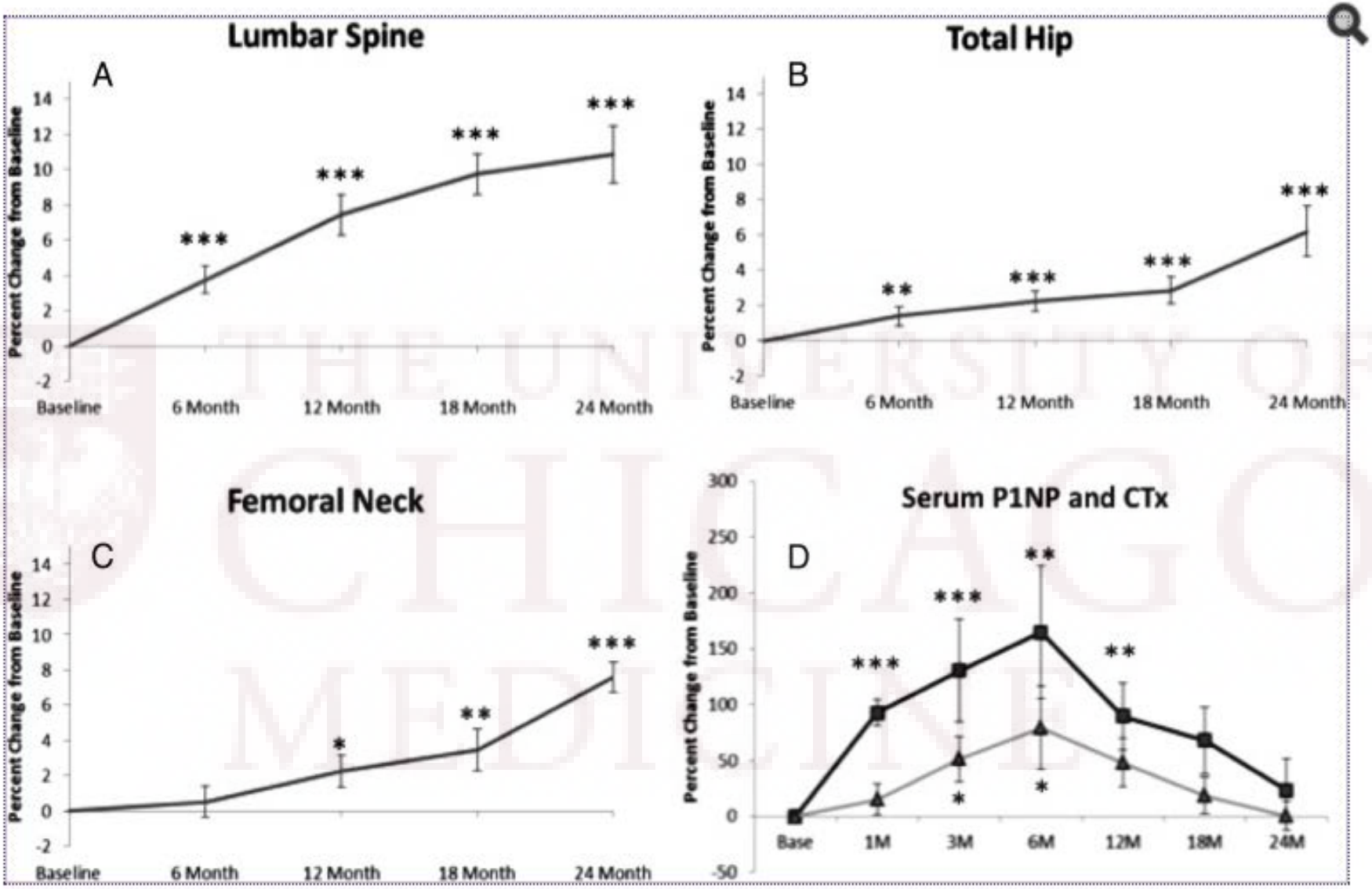
- **Study:** Open-label pilot
- **Population:** 21 premenopausal women with unexplained fragility fractures or low BMD
- Teriparatide 20 µg daily for 18 to 24 months
- Primary endpoint: within-subject percent change in lumbar spine BMD
- Secondary endpoints: percent change in hip and forearm BMD, transiliac biopsy parameters (trabecular bone volume, microarchitecture, stiffness, and adipocytes), serum N-terminal propeptide of procollagen type 1 (P1NP), and C-telopeptide

Cohen A, JCEM. 2013

Management

- BMD increased at the spine (10.8 ± 8.3%) total hip (6.2 ± 5.6%), and femoral neck (7.6 ± 3.4%) (all $P < .001$)
- Transiliac biopsies demonstrated significant increases in cortical width and porosity and trabecular bone volume and number increased, mirrored by a 71% increase in trabecular bone stiffness ($P < .02$)
- Four women had no increase in BMD

Cohen A, JCEM. 2013



- BMD and bone turnover markers after teriparatide: percent change from baseline: A, Lumbar spine. B, Total hip. C, Femoral hip. D, Bone turnover markers serum P1NP (■) and serum CTx (▲). **P* < .05; ***P* < .01; ****P* < .001; significant percent change from baseline

Cohen A, JCEM. 2013

Management

- Just as in postmenopausal women, discontinuing teriparatide results in bone loss and therefore should be followed by antiresorptive therapy
- Pregnancy and lactation: a very common cause of bone loss

Cohen A, JCEM. 2015

Back to our patient

- She was diagnosed with low bone density at age 26 (before lungs transplant) and got worse after lungs transplant with chronic inflammation, malabsorption, low PO intake and steroids use all likely contributing
- Review her DEXA scan, she has been having stable bone mineral density compared to last year
- Her z-score at spine was in low bone density for age range but her hip was still above -2.0
- Conservative treatment
- Will contact provider if develops fall, fracture, or plan for pregnancy

Conclusion

- Conservative therapy is best for young women
- Management of osteoporosis in premenopausal women with secondary osteoporosis should focus on diagnosis and specific targeted therapy of the secondary cause
- Pharmacologic therapy should be reserved for the most severely affected women, who have very low BMD (*z* scores -2.5), declining BMD on conservative therapy or major fractures

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