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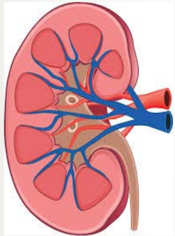
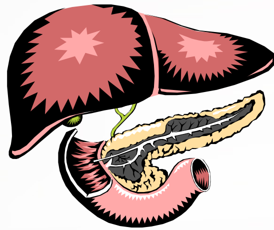
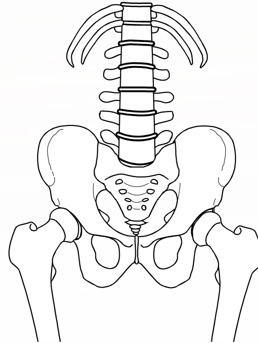
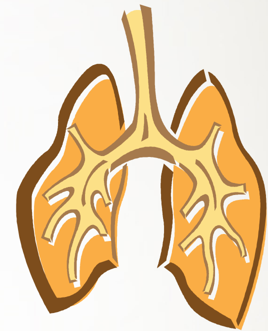
Update: Osteoporosis & The Transplant Patient



Bobo Tanner MD
Nichole Bonzano PA-C
Vanderbilt Osteoporosis Clinic
Division of Rheumatology
Oct 10,2022

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BT Disclosures

Research support ,advisory panel and /or speakers bureau:

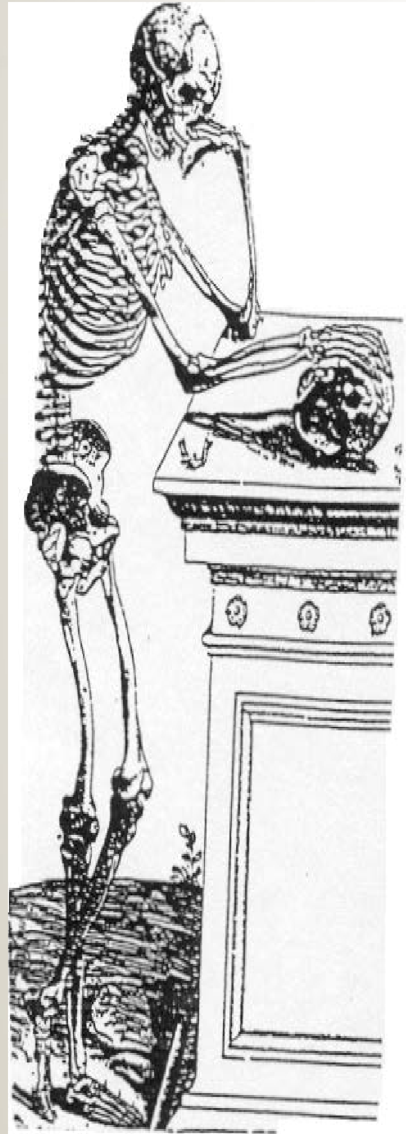
Amgen , Ultragenyx

Data from the United Network for Organ Sharing (UNOS)

2021 Organ Transplants in US:

- 41,354 transplants, deceased & living donors
- First time to exceed 40,000
- Kidney :24,669
- Liver : 9,236
- Heart: 3,817
- Lung: 2,524
- Pancreas/kidney: 963
- Intestine:96
- 106,962 on the wait list, lowest since 2009

Agenda



Why are you thinking about bone?

- Osteoporosis overview
- DXA Bone density testing
- Labs
- Medications & Management
- Cases & Organ Specific issues
- Take home points
- Case

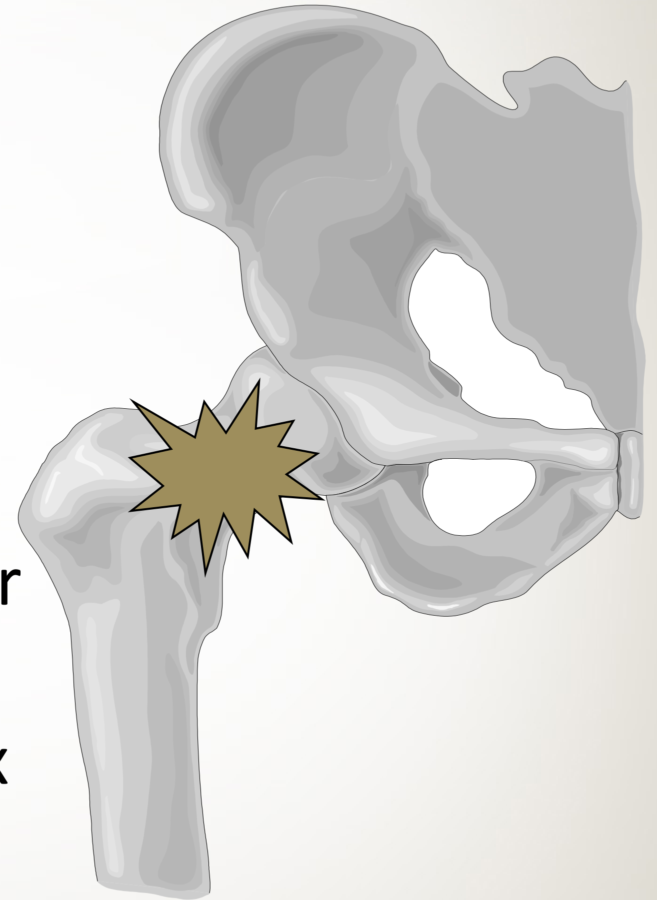
Transplantation Associated Osteoporosis (TAOP)

- 3-11% bone loss 1st yr. post transplant
- 14-36% increase incidence of fragility fxs.
- Most fractures occur at relatively normal Bone Mineral Density:
  - Bone Quality? Bone turnover?
- Pre-transplant risks: fracture, chronic disease & glucocorticoids (GCS)
- Post-transplant risks : GCS & calcineurin inhib.
  - Controversy: cyclosporine A & tacrolimus
  - tacrolimus better?, may allow less GCS
- Relatively few guidelines for care
  - ISHLT 2010
  - Dr Rosen and Dr. Shane give their experience on UpTo Date

Carbonare et al Transplantation 2011

Hip Fracture: Devastating Event

- Mortality rate same as breast cancer
- 20% excess mortality in the first year
- 50% incapacitation
- 20% of females need assisted living or nursing home
- 80% of 75 yo preferred death to hip fx & nsg hm
- Cooper C, et al. *Am J Epidemiol*. 1993;137:1001



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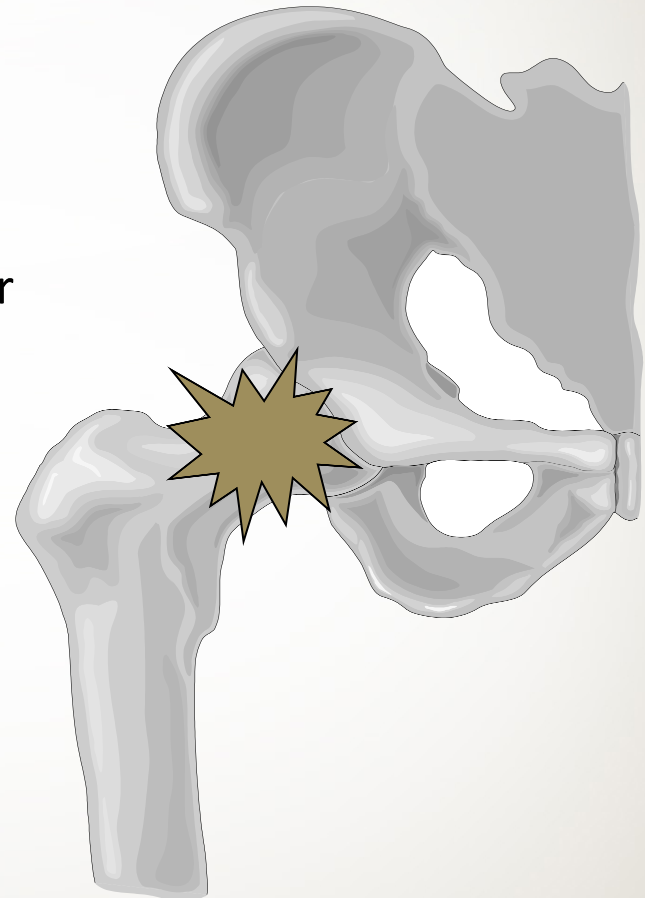
Hip Fracture: Devastating Toll: "The 4 Ds"

1. Death[2,6]
   Mortality rate same as breast cancer
2. Disability[1,2]
   50% incapacitation
3. Dependence[1,2]
   20% of females need assisted living or nursing home
4. Delirium & dementia[3,4,5]
   40% to 60% risk of delirium
   41% higher rate of dementia



[1] www.share.iofbonehealth.org/WOD/2012
[2] Cooper C, et. al., Am J Epidemiol 1993;137:1001
[3] Gustafson et al. . *J Am Geriatr Soc* 1988;36:525–530.
[3] Givens et al *J Am Geriatr Soc*. 2008 Jun;56(6):1075-9
[4] Tsai C et al, *Medicine 2014* 93(26) :1-7
[5] Marcantonio et al *J Am Geriatr Soc.* 2011 Nov;59 Suppl 2:S282-8
[6] Panula et al BMC Musculoskeletal Disorders 2011, 12:105

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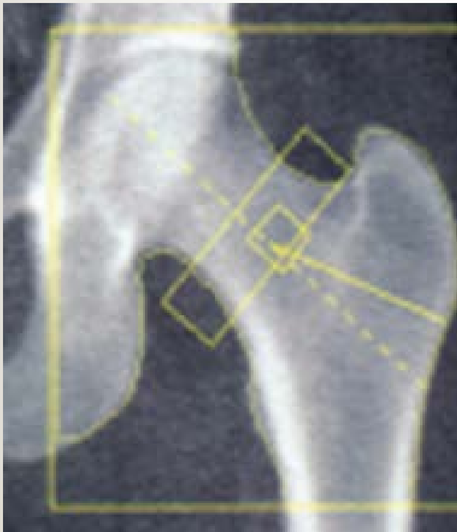
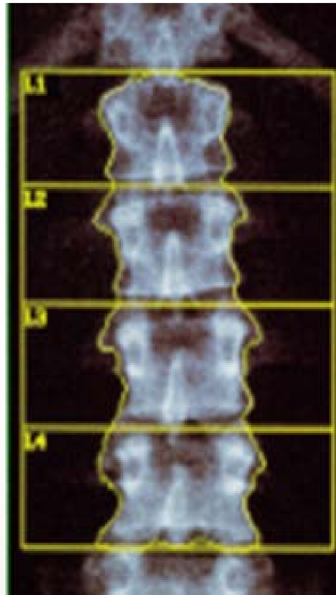
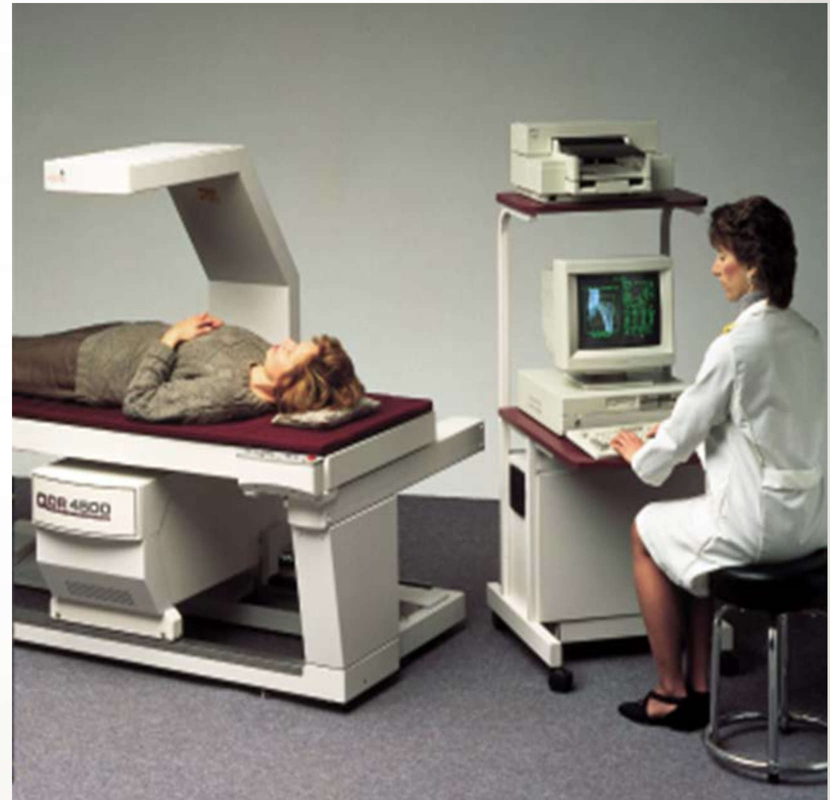
When should DXA Bone Density testing be performed?







Reasons **Medicare** Will Reimburse for **DXA Bone Density Testing**

1997 Bone Mass Measurement Act

1. Women with estrogen deficiency (E28.39)*
2. Spine x-ray evidence of fracture or OP (M48.54XA)*
3. **Glucocorticoid therapy (3mos, 5 mg/d) (Z79.52)***
4. Primary Hyper-PTH (E21.0)*
5. Follow-up OP treatment (23 months unless medical reason for **sooner e.g. steroids**) (M81.0)*

**Note: ICD 10 codes are examples and may not work for your Medicare local carrier*

Federal Register 1997 for HCFA/CMS
Medicare Osteoporosis Measurement Act 2003

When to Order DXA Bone Density testing

Before transplantation:

- Transplant candidates increased incidence of bone disease vs. general pop
- Evaluate and manage before the transplantation
- **DXA on all candidates ,lumbar spine, femoral neck, total hip, 33% radius**
- Calculate FRAX, Trabecular Bone Score (DXA software)
- X-rays: thoracic & lumbar spine, or vertebral fracture assessment (VFA) by DXA, screen for occult vertebral fractures, esp. 1.5” ht. loss, or chronic steroids
- Note risks factors for fracture & poor bone health: alcohol abuse, chronic smoking, hypogonadism, medications: glucocorticoids, heparin, loop diuretics.
- Labs: see later slide

A normal Bone Density does not protect against post transplant fractures

Repeat DXA yearly while on glucocorticoid treatment

Chandran C et al, Transplantation Osteoporosis. NCBI Bookshelf ,Stat Pearls, 2021. PMID:33232003

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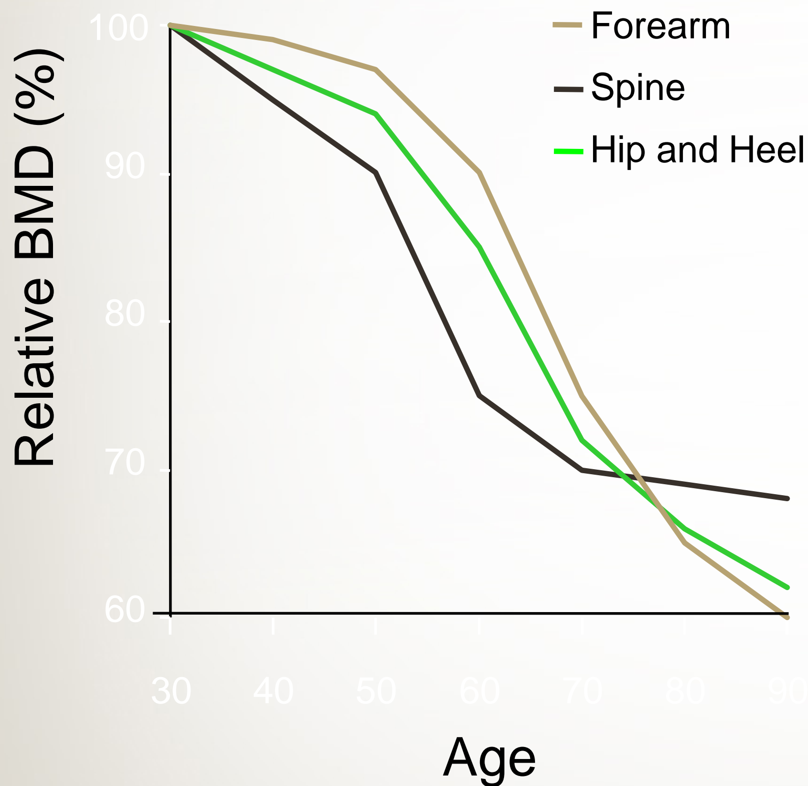
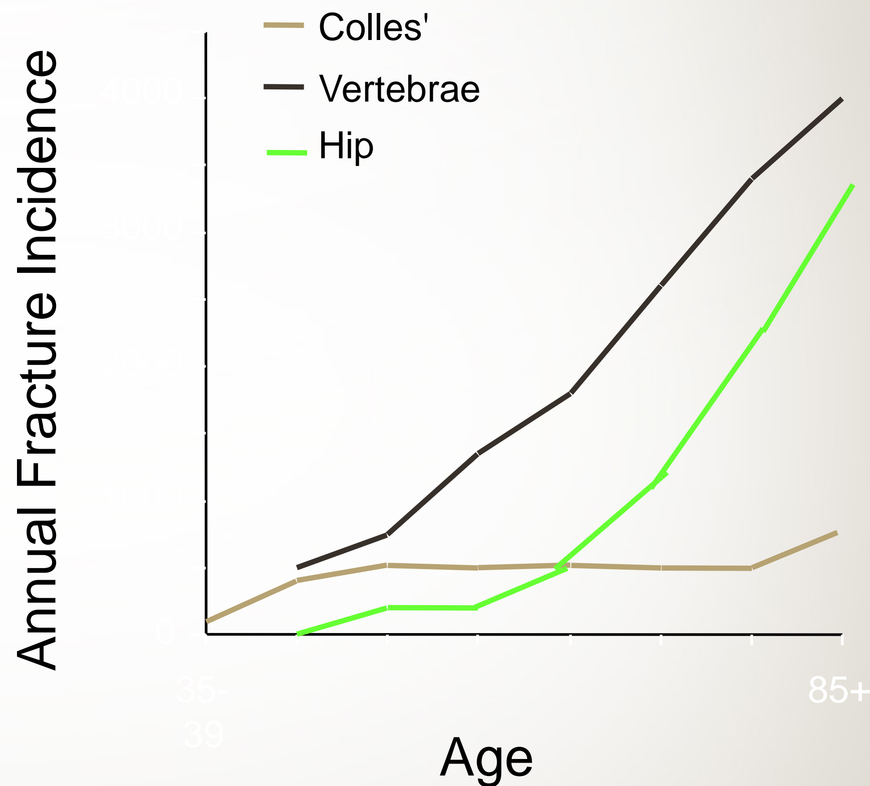
As T-scores(BMD) Get Worse ,Fracture Risk Increases

- *Remember: Only ~1/3 of spine fractures are acutely painful*





Faulkner KG. *J Clin Densitom.* 1998;1:279–285.

Cooper C. *Baillières Clin Rheumatol.* 1993;7:459–477.

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How Do You Interpret DXA Bone Density Results?

World Health Organization DXA Classification

	T-score *Postmenopausal women, men≥50*
Normal	≥ -1
Osteopenia	< -1 and > -2.5
Osteoporosis	≤ -2.5
Severe Osteoporosis	≤ -2.5 with Fracture

WHO Study Group, JBMR 1994

Bone Health Lab Tests

Usual Transplant labs (CBC, CMP) and:

- 25-OH Vit D
- PTH
- TSH
- Magnesium
- Phos
- Bone Specific Alk Phos
- P1NP
- tTG/celiac panel
- serum Free Light Chains
- SPIEP
- 24 hr. urine Ca & creat. , UPIEP

Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporosis International. 25(10):2359-81, 2014. PMID: 25182228

3 Rare Bone Conditions Not to Miss

1. Hypophosphatemia- low serum phos ,bone/muscle pain, fractures, high urine phos, elevated FGF -23 hormone: look for mesenchymal tumor, resect for cure
2. Hypophosphatasia-low serum alkaline phosphatase($\leq$30), fractures, elevated Vit B6, abnml ALPL gene; treat with asphotase-alpha to stop fractures
3. Hypoparathyroidism- low serum calcium, low PTH level, treat with 1-84 PTH to stabilize

Non-Prescription Treatment for Bone Health and Fracture Prevention

1. Correct Vitamin D levels,25-OH Vitamin D above 30ng/mL, with vitamin D3

2. Get adequate calcium through diet ~1,000mg daily, 600mg max per serving, use calcium citrate to "fill in gap"; verify with 24 hr urine, it does not help to take more calcium than needed

3. Exercise & Tai Chi , to provide a mechanical load to bone and for improved balance

4. Avoid cigarette smoking and heavy alcohol consumption

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Osteoporosis Medications

- Goal: reduce risk of fracture
- Antiresorptive medications:
- Bisphosphonates: *Beware Renal(eGFR $\geq$35) & GI (GERD,stricture)*
    - Oral: alendronate , residronate, ibandronate
    - IV : zoledronate (Reclast®)
  - Denosumab (Prolia®) *subcut. every 6 months*
- Anabolic drugs: <u>Ideally Use First</u>
  - teriparatide (Forteo®),*self injection nightly, x 2yrs*
  - abaloparatide (Tymlos®), *self injection nightly, x 2 yrs*
  - romosuzumab (Evenity ®)*subcut,office,monthly x 1 yr*

Medication Side effect Concerns

- Osteonecrosis of Jaw: rare, post invasive dental work, use chlorhexidine mouth wash , abx (bisphosphonates & densoumab),f/u
- Atypical femur fracture: rare, after 4-5 years treatment, “drug holiday”, ask about thigh pain (Bisphos. & densoumab)
- Osteosarcoma:(theoretical) PTH analogues & radiation
- Hypercalcemia: anabolic medications
- Hypocalcemia : denosumab, renal patients
- MI & CVA: romosuzumab

Denosumab (Prolia®) in Transplant Patients

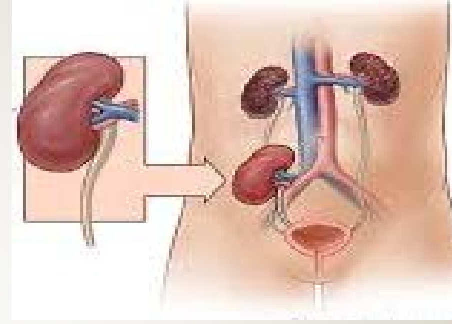
- No dose adjustment for renal insuff. But if CrCl <30 monitor for hypocalcemia
- Rebound bone loss and fracture risk upon cessation: **Need An Exit Strategy**
- Czech study: 63 Kidney Tplant pts. Dmab ~2 years showed efficacy and no safety issues
- Swiss study: 90 Kidney Tplants vs. std care , Dmab x2 doses, increased BMD, bone strength, quality , (HRpQCT, TBS), but more frequent UTIs, not pyelonephritis or urosepsis.

Buckley et al, ARTHRITIS & RHEUMATOLOGY Vol. 69, No. 8, August 2017, pp 1521–1537
Brunova J et al. Front. Endocrinol. 2018. 9:162.doi: 10.3389/fendo.2018.00162
Bonani M et al. Am J Transplanat.2016 ;16(6):1882-1891
Bonani M et al. Transplantation. 101(9):2139–2145, SEPTEMBER 2017
Bonani M et al. Nephrol Dial Transplant. 2019 Oct 1;34(10):1773-1780

Long term monitoring

- Labs: Vit D, calcium, creatinine, P1NP
- Annual DXA bone density (hips, spine, 33% radius)
- Bone Turnover Markers (PINP, Bone Spec. Alk Phos, C-Telopeptide)
- X-rays /MRI if height loss, back pain, thigh pain
- Re-evaluate , maybe change medication if worse
- Consider “drug holiday”

Kidney Transplant Patients



Bone loss: greatest in 1st 6-18 months post txp, 4-9%

Assoc. with low estradiol & testosterone, not always gender , age, GCS, rjxn, PTH

Fractures: risk factors :previous fracture, age, diabetics,

locations: hips, long bones, feet vs. spine & ribs

Post transplant: 34% increase in hip fractures compared to continued dialysis pts.

Treatment concerns: Bisphosphonates & possible renal toxicity

Teriparatide/abaloparatide & hyperparathyroidism

Denosumab & hypocalcemia

Labelled bone biopsy sometimes required in renal transplant patients to evaluate for adynamic bone prior to bisphosphonate therapy

Vangala C, et al Front Med (2018) 5:211. doi: 10.3389/fmed.2018.00211

Kidney/Pancreas T'plant Case

64 yo female , school administrator

- Age 50 **kidney and pancreas transplant,** steroids per protocol.

Fracture history & DXA:

- Age 51-64 :**distal radius fx,** femoral condyle fx, **prox humerus fx, wrist fx**
- Age 51 DXA, lumbar spine L1-L2 1.0, femoral neck -1.9, total hip -1.4.
- **Age 64 DXA, l**umbar spine L1-L2 -0.3, **femoral neck -2.9, total hip -2.7**

Nutrition & labs:

- Age 56 VEGAN.
- Age 58 Vitamin D deficiency, level was 24, age 60 was 23, at 64 is 19
- Parathyroid hormone elevated at 177

Other risk factors**:** Age 15 Type 1 diabetes , resolved after transplant.
Severe HAs, sees Neuro, punctate lesions on MRI

Kidney/Pancreas T'plant Case

- Next?
- Labs?
- Treatment?
  - non-prescription
  - Rx
- Next DXA ?
- Other monitoring?

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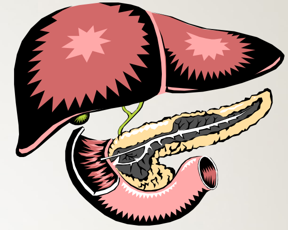
Liver Transplant Patients



Bone loss:
3.5-24% in first year
Risk factors: Previous fracture
High MELD scores,
Low BMI,
Post menopausal
Older age

Fractures:
24-65%
Ribs and spine most common
Highest in 1st 6-12 months
Risk factors: Prior fracture, Prednisone dose, Women with PBC

Treatment issues: Liver activates vitamin D to 25-OH Vitamin D
Bisphosphonates have been used in PBC
IV Zoledronate 4mg baseline,then1,3,6,9 months after transplant prevented bone loss

Crawford BAL et al *Ann Intern Med.* 2006;144:239-248
Abate et al *Endocrine Practice* 27 (2021) 426-432
Yadav et al *Nutr Clin Pract* 2013 28: 52

Liver Transplant Case

61 yo female, retired

Age 60 liver transplant for alcoholic cirrhosis, steroids per protocol

Fracture history: age 60 fall, left tibia fracture, healed with boot.

DXA

- Age 60 (pre-tplant) **DXA,** lumbar spine -1.6, femoral neck -1.1, total hip -0.3, RX alendronate, GI upset
- Age 61 post tplant **DXA** Lumbar spine L1-L2 -1.4, femoral neck -1.6 (0.815), total hip -0.8
- **FRAX: 22% MO**F, 2.6% hip fracture risk. BHOF guidelines she would benefit from receiving treatment to reduce her risk of fracture.

Labs : post tplant

24-hour urine calcium, normal at 126 mg.

Vitamin D is 35

Hypomagnesemia, level was 1.5. now on MG supplement

CKD 3b, eGFR 39

Liver Transplant Case (cont'd)

- Next?
- Labs?
- Treatment?
  - non-prescription
  - Rx
- Next DXA ?
- Other monitoring?

Heart Transplant Patients

Bone loss: 3-11% in first year

Fractures: 14-36% in first year,
22-35% long term
fractures occur at osteopenic T-scores (-1.5)

Treatment issues: 92% vitamin D deficient
20% CKD III

Stein et al .Clin Transplant. 2009 Nov-Dec; 23(6): 861–865

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ISHLT Heart Transplant Guidelines 2010

Pre-transplant

- Screen & treat all candidates
- Spine x-ray adults to screen for vert. fractures
- Target Vit D level 30ng/mL
- Baseline DXA for adults
- Rx Bisphosphonates for OP
- Calcium, physical activity

Post Transplant

- Rx Bisphosphonates first year
  - Activated vit D is not first line Rx
  - Don't use Calcitonin
- DXA again a 1 year
- If ≥-1.5 & no GCS: stop bisph.
- DXA again 2 yrs if osteopenia
- DXA again 3 yrs if nml
- Monitor for fractures

Note : Guidelines were pre denosumab, abaloparatide and trabecular bone score

Costanzo et al J Heart Lung Transplant 2010 Aug 29 (8):915-56

Case

- 69 yo w ♀
- Age 26- TAH, BSO; Rx estrogens "few years"
- Age 33- DXA Bone Density test= "low"
- Failed treatments:
  - SQ calcitonin-GI
  - alendronate -GI
  - raloxifene–Hot flashes
- Age 50: Ischemic heart dz
- Age 55- DXA hip T-score= -3.5
  - Rx risedronate x 2yrs
- Age 57: Cardiomyopathy
- Heart T'plant list

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Case (cont'd)

- Age 59- cardiac transplant
  - prednisone 5mg/day
  - re-started risedronate = GI issues
  - switched to ibandronate
- Age 64 DXA Femoral Neck T-score = -2.4
- What would you do next?
  - Optimize vit D & calcium?
  - Stop ibandronate?
  - Switch to anabolic medication?
  - "Drug holiday" and monitor DXA?
  - Request bone health consult?

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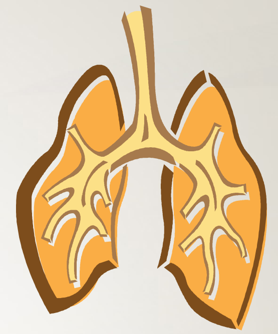

Lung Transplant Patients

Bone loss: 2-5% in first year
37% osteoporosis at time of t'plant (previous steroids)

Fractures: 18-37% in first year
fractures occur at T-score of -1.5

Treatment issues: often an opportunity to treat before t'plant

Shane et al. Am J Med. 1996 Sep;101(3):262-9.
Hariman et al. Journal of Osteoporosis .2014, http://dx.doi.org/10.1155/2014/573041

Bone Health & Solid Organ Transplantation:

2019 ECTS Recommendations

- Glucocorticoids(GCs): use lowest dose possible for graft survival
- Tacrolimus may limit GCs use;more modest BMD reduction than cyclosporine
- Sirolimus & everolimus (mTOR inhibitors), reduce bone turnover, mostly decreased resorption & reduce GCs use, good for bone
- Other meds, MMF, may reduce GCs, therefore good for bone.

Anastasilakis A D et al.Bone 2019 Oct;127:401-418

Bone & Solid Organ Transplantation:

2019 ECTS Recommendations (cont'd)

- Kidney: KDIGO CKD-MBD 2017 guidelines:
  - first 12 months p tplant, eGFR > 30 ml/min, low BMD:
  - Consider vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents, possible labelled bone bx
  - After that year, what next?
- Liver: pre-tplant DXA, spine x-ray, again 3-6 mos p tplant, may require more Vit D, start BPs early p tplant, DMAB if renal insuff or can't take BPs, Dmab well-tolerated ,increased BMD p tplant liver, kidney, pancreas
- Heart: Pre-plant labs, DXA spine x-ray, correct Mg; Rx BPs p tplant
- Lung: Pre-tplant DXA , spine imaging, Vit D ,BPs

Anastasilakis A D et al. Bone 2019 Oct;127:401-418

Pediatric Transplant Patients

- Long term survival after t'plant
- 6 X incidence of fx compared to healthy pop.
- High risk for vertebral fractures & scoliosis
- Delayed growth and skeletal maturation
- DXA hard to interpret:short stature, skeletal delay
- DXA scores don't correlate well with fracture risk
- Bone biopsies decreased bone turnover, high matrix mineralization.

Fratzl-Zelman et al JBMR May 2017. 32(5): 1116–1125

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When Should I Refer A Patient To An Osteoporosis Clinic?

- When you do not feel comfortable treating with osteoporosis medications
- When the patient has not tolerated OP meds
- When a patient has already been taking an oral bisphosphonate for 3-5 years
- When a patient has CKD 3b or worse
- When a patient continues to have fractures
- Unexplained or difficult to treat bone related labs

3 Reasons Patients Object to Taking Osteoporosis Medications

1. Cost
2. Fear of medication side effects
3. Lack of understanding about risks of osteoporosis and fractures

Often, they want someone to sit and review these details with them

"Don't believe everything you read on the internet"- *Abraham Lincoln*

Take Home Points

- Fractures affect morbidity & mortality
- Transplants increase fracture risk
- Evaluate bone health pre-transplant and treat
  - DXA, Labs, nutrition, exercise, fall prevention
- A normal DXA Bone Density does not protect against post transplant fractures
- Height loss may be the only sign of a compression fracture
- Anabolic meds work best if used first
- All medications require monitoring and are not used forever

- Questions for us?

Resources:

- www.NOF.org Bone Health and Osteoporosis Foundation
- www.ISCD.org Internat. Soc. Clinical Densitometry
- www.IOF.org Internat. Osteoporosis Foundation

Thank you for concern about your patient’s bone health!