

Bone Health after Bone Marrow Transplant

Celebrating a Second Chance at Life Survivorship Symposium

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Disclosures

- **None related to this talk**
- **Research funding**
 - Ipsen/Clementia
 - Incyte
 - Regeneron (past)

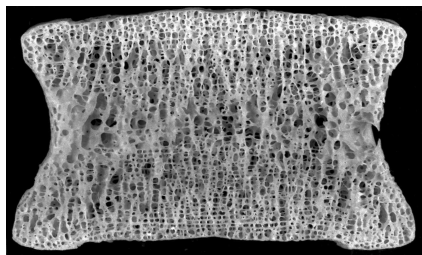
Objectives

- Review definition of low bone mineral density (BMD) and osteoporosis
- Describe prevalence of low BMD and fractures with hematopoietic cell transplant (HCT)
- Identify factors that contribute to low BMD
- Review guidelines for the screening and management of low BMD

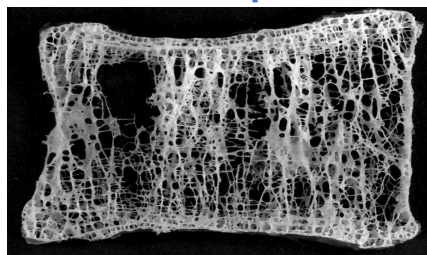
What is Osteoporosis?

- “Porous” bone
- Bone that is low in density
- Bone that is weak
- Bone that is at high risk of breaking

Normal



Severe Osteoporosis



Symptoms of Osteoporosis

- Silent disease until a fracture occurs
- Major public health problem
 - Over 50 millions Americans have low BMD or osteoporosis
 - 2 million osteoporosis-related fractures annually
- Osteoporosis-related fractures
 - Increase in mortality
 - Increase in morbidity (pain, loss of independence, respiratory and GI issues)
 - Significant health-related cost
- Continues to be under-diagnosed and treated

Who is at risk?

- Family history of osteoporotic fracture or hip fracture
- Current smoking
- Low BMI
- Personal fracture history
- Excessive alcohol, caffeine or soda intake
- Medications: **prednisone**, high dose proton pump inhibitors, seizure medication
- Medical conditions: **early menopause, low testosterone in men, diabetes, celiac disease**

Screening for Osteoporosis

Important for primary prevention of fracture

Dual Energy X-Ray Absorptiometry (DXA)

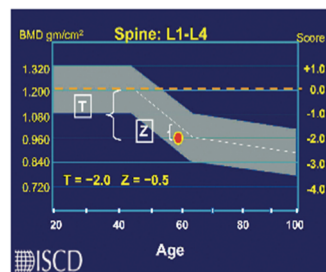
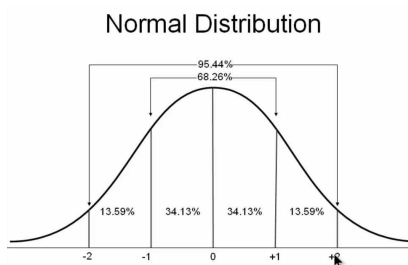
Non-invasive, very low dose of radiation

Measures the bone mineral density (BMD) and compares it to a normative database



DXA Interpretation

- **Z-score: standard deviation variance of bone mineral density (BMD) from the mean BMD of the *age matched* adult reference population**
- **Z-scores are used in pre-menopausal women and men <50 yrs**
 - **Z-score at or below -2.0 is defined as below what is expected for age**



DXA Interpretation

T-score: standard deviation variance of bone mineral density (BMD) from the mean BMD of the **young adult** reference population

T-scores are used for post-menopausal women and men >50 yrs

Normal

T-score at -1.0 and above

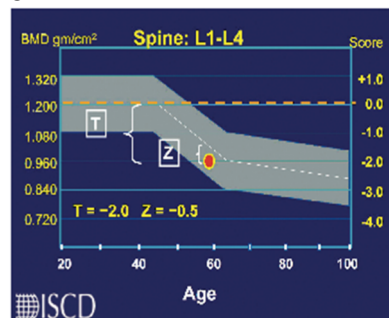
Low bone mass (“osteopenia”)

T-score between -1.0 and -2.5

Osteoporosis:

T-score at or below -2.5

Patients in this group who have already experienced one or more fractures are deemed to have severe or “established” osteoporosis



From: ISCD Bone Densitometry Clinician Course, Lecture 5 (2008).

How is Osteoporosis Diagnosed?

- T-score ≤ -2.5 on DXA scan in post-menopausal women and men >50 yrs
- History of fragility fractures
 - Especially compression fractures and hip fractures
 - Regardless of DXA results
- High risk of fracture based on clinical country specific calculation tools (ie FRAX)
 - 10 yr probability of fracture (US)
 - $\geq 20\%$ for all osteoporotic fracture
 - $\geq 3\%$ for hip fracture

FRAX (Fracture Risk Assessment Tool)

<https://www.shef.ac.uk/FRAX/>

Country: **US (Caucasian)** Name/ID: [About the risk factors](#)

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
 Age: Date of Birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

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/cm³)
 T-Score

BMI: 24.2
 The ten year probability of fracture (%)
with BMD

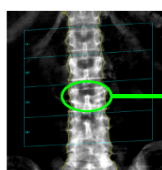
Major osteoporotic	13
Hip Fracture	3.2

If you have a TBS value, click here:

Trabecular Bone Score (TBS)

- TBS is a texture parameter related to bone micro architecture that may provide more skeletal information not captured by DXA
- TBS can be used in association with FRAX and BMD to adjust FRAX-probability of fracture in post-menopausal women and older men

Bone Mineral Density images



Identical BMD



Illustration of a good microarchitecture

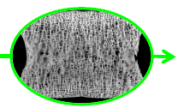
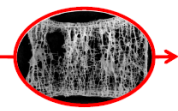
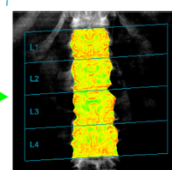


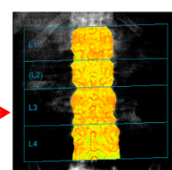
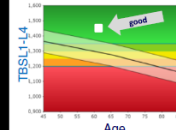
Illustration of a poor microarchitecture



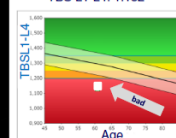
TBS Images and associated reference curves



TBS L1-L4: 1.457



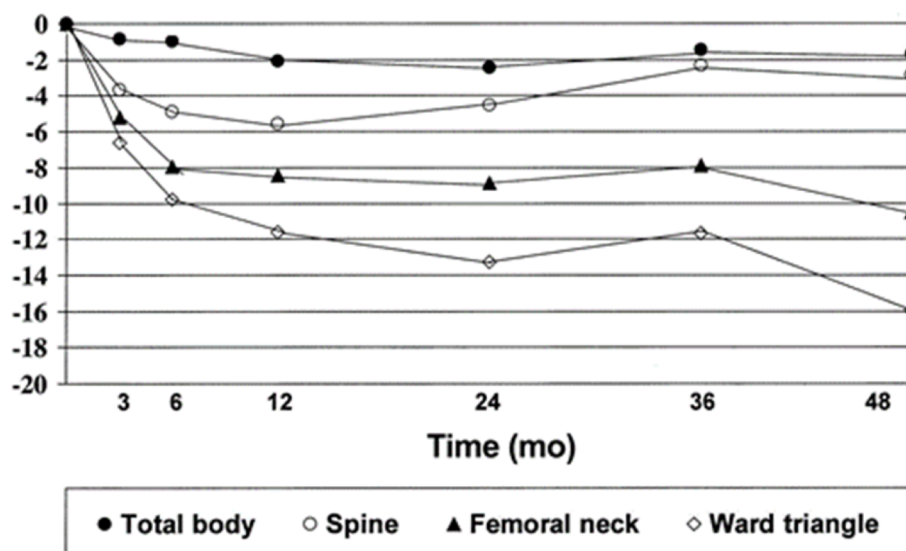
TBS L1-L4: 1.132



Osteoporosis Summary

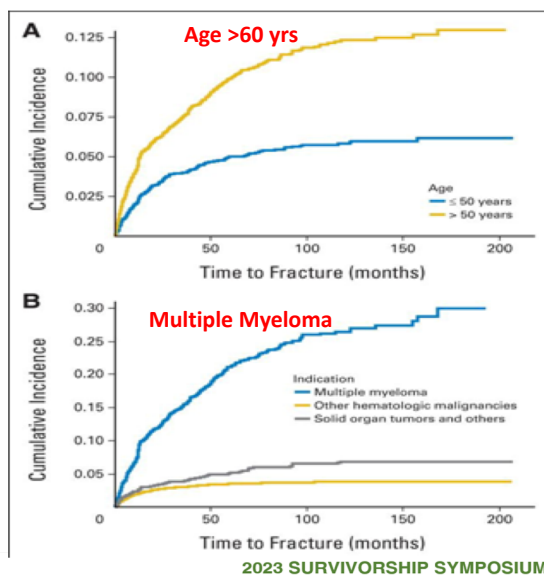
- Osteoporosis is common
- Affects both men and women
- Silent disease
- Important to screen using DXA prior to a fracture occurring

Bone loss after Hematopoietic Cell Transplant



Fracture Risk with Transplant

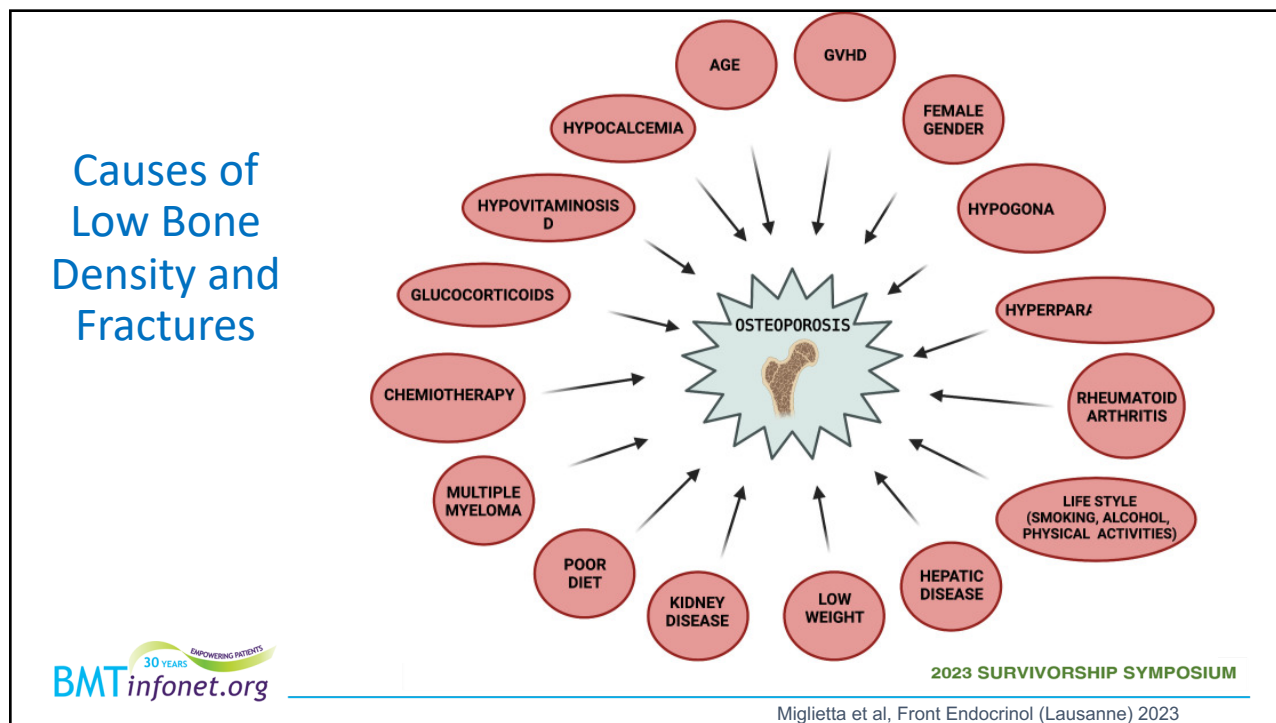
- Retrospective Study >7,000 patients
- Compared to US general population
 - ~8 fold increase in fracture risk



Pundole et al J Clin Oncol 2015

Summary of Bone Changes with HCT

- BMD changes occur in first 6-12 months
- Some recovery in spine BMD, less in hip
- Short-term bone loss greater in patients who received donor cells (allogenic)
 - Prolonged and greater post-transplant cytokine release
 - Graft Vs Host Disease
 - Frequent use of immunosuppressive treatments in the allogeneic setting
- Increased risk of fracture especially in the older population



General Guidelines

- Calcium:
 - Total calcium intake 1000-1200 mg daily
 - No more than 500-600 mg from supplements
 - Calcium citrate if patient is on proton pump inhibitors
- Vitamin D
 - Vitamin D3 800 units daily
 - Aim for 25-OH Vitamin D >30 ng/ml
- Fall prevention, physical therapy and early mobilization
- Smoking cessation
- Lowest dose of prednisone
- Regular weight bearing exercises

Consider Following Guidelines

- Pre-transplant DXA
 - All adult patients age 40 or above
 - Younger
 - Prednisone >5 mg/day for 3 months
 - Fracture history
- Post-transplant DXA
 - Check DXA 3-12 months after transplant for all
 - Consider serial DXA scan every 1-2 yrs
 - Ongoing steroid use
 - Z-score <-2.0
- Pharmacological therapy
 - Pre-transplant T-score <-1.5
 - Osteoporosis or fractures history or high risk of fracture
 - Significant bone loss on serial DXA

Pharmacological Therapy; Decrease Bone loss

	Hip Fracture Reduction	Spine Fracture Reduction	Adverse Effects/Contraindication
Bisphosphonates (oral once a week; IV ZOL yearly)	40%	50-70%	Orals: Esophageal GVHD IV: flu-like symptoms, Renal Dysfunction AFF/ONJ
Denosumab (Prolia) (s/c every 6m)	40%	68%	Infections hypocalcemia AFF/ONJ Rebound Bone loss
Estrogen	34%	34%	Breast cancer, stroke, MI, blood clots

Pharmacological Therapy; Stimulate Bone Formation

	Hip Fracture Reduction	Spine Fracture Reduction	Adverse Effects/ Contraindication
Teriparatide (Forteo) (s/c injection daily x 2yrs)	No evidence	65%	Hypocalcemia hypotension History of skeletal radiation Children with open growth plates
Abaloparatide (Tymlos) (s/c injection daily x 2yrs)	No evidence	86%	Similar to Teriparatide
Romsozumab (Evenity) (s/c injection monthly x12m)	No evidence	73%	Hypocalcemia, stroke, MI AFF/ONJ reported

Pharmacological Therapy

- Bisphosphonates
 - First line therapy
 - Most studied in transplant patients
- Denosumab studied in 33 females only
- Estrogen is recommended in young women with hypogonadism
- No studies using Teriparatide
- No studies using Abaloparatide
- No studies using Romsozumab

Bisphosphonates

Generic name	Brand name	Route	Dosing
Alendronate	Fosamax (plus D) Binosto	Oral	10 mg daily 70 mg weekly
Risedronate	Actonel Atelvia	Oral	5mg daily 35 mg weekly 150mg monthly
Ibandronate	Boniva	Oral/IV	2.5 mg daily 150 mg monthly 3mg IV q3 months
Zoledronic acid	Reclast	IV	5mg yearly

Adverse Effects: Bisphosphonates

- Short-term:
 - GI side-effects: difficulty swallowing, inflammation of the esophagus and gastric ulcer (orals)
 - Increase in creatinine: IV Zoledronic Acid
 - Flu-like illness: IV Zoledronic Acid
- Long-term:
 - Atypical fracture of the femur ~3-100/100,000
 - Osteonecrosis of the jaw (ONJ) ~1-10/100,000
 - Reported mainly in cancer patients receiving IV bisphosphonates (1-10/1,000)



Summary

- Osteoporosis and fractures are common in the general population and are associated with significant morbidity and mortality
- HCT is associated with bone loss
- HCT is associated with increased fracture risk, mainly due to glucocorticoids
- Bisphosphonates prevent bone loss associated with HCT



QUESTIONS?



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