

Osteoporosis

Compromised Bone Strength
Predisposing to Increased Risk of
FRAGILITY FRACTURES

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Disclosure

Michael McDermott has no conflict of interest or relationships to disclose in relation to this educational activity.

Learning Objectives

- Discuss the diagnosis and evaluation of osteoporosis.
- Explain the individualized approach to managing osteoporosis according to degree of fracture risk.
- Review treatment of vitamin D deficiency in people with normal intestinal absorption and in those with malabsorption disorders.

Osteoporosis

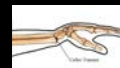
Fragility Fractures (Low Trauma)



Vertebral Fractures
700,000/year
2/3 Asymptomatic

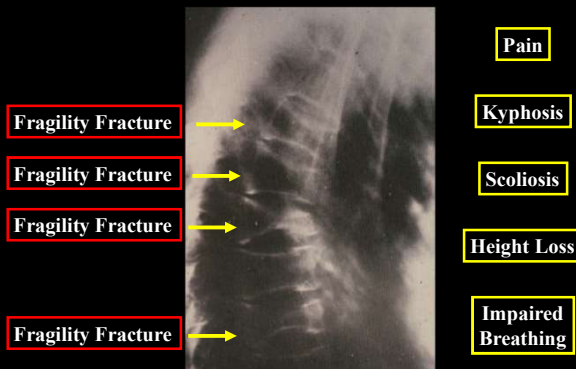


Hip Fractures
300,000/year
Disability/Mortality High



Wrist Fractures
250,000/year

Vertebral Fractures



Osteoporosis Diagnosis

Fragility Fracture Criteria

Presence Of:



Vertebral Fracture

Hip Fracture



Fragility Fractures = Osteoporosis
Bone Density Testing Not Required for Diagnosis

Osteoporosis Diagnosis

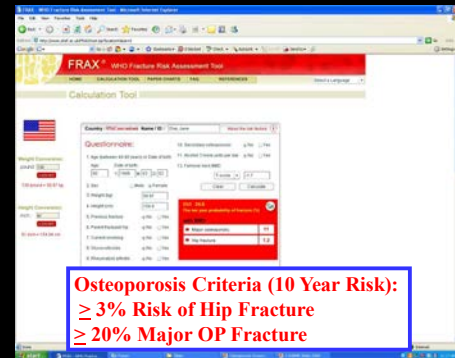
Bone Densitometry Criteria

- | | <u>T-Score</u> |
|----------------|----------------|
| ▪ Normal | > -1.0 |
| ▪ Osteopenia | -1.0 to -2.5 |
| ▪ Osteoporosis | < -2.5 |

Overall Diagnosis: Made by T-Score at Lowest Site

Osteoporosis Diagnosis

FRAX Risk Criteria



Osteoporosis Criteria (10 Year Risk):
 ≥ 3% Risk of Hip Fracture
 ≥ 20% Major OP Fracture

Low Bone Mass and Fractures are Not Always Osteoporosis

**Evaluate for Secondary or
Contributing Causes**

Differential Diagnosis

Causing / Contributing To Osteoporosis

- | | |
|---------------------------|-----------------------------|
| ▪ Osteomalacia | ▪ Eating/Exercise Disorders |
| ▪ Osteogenesis Imperfecta | ▪ Inflammatory Bowel Dz |
| ▪ Hyperparathyroidism | ▪ Primary Biliary Cirrhosis |
| ▪ Hyperthyroidism | ▪ Multiple Myeloma |
| ▪ Hyperprolactinemia | ▪ Rheumatoid Arthritis |
| ▪ Hypogonadism | ▪ Chronic Renal Failure |
| ▪ Cushing's Syndrome | ▪ Idiopathic Hypercalciuria |
| ▪ Celiac Disease | ▪ Systemic Mastocytosis |

High Risk Medications

Established: Glucocorticoids, Thyroid Hormone Excess,
Anticonvulsants, Androgen Deprivation Rx.
Probable: SSRIs, Proton Pump Inhibitors.

Osteoporosis Evaluation

Secondary or Contributing Factors

Lab Tests

- | | |
|-------------------------------------|------------------------|
| ▪ Calcium | Calcium ↑ or ↓ |
| ▪ Creatinine | ▪ PTH |
| ▪ Alkaline Phosphatase | Anemia, Protein Gap ↑, |
| ▪ 25 OH Vitamin D | or Calcium ↑ and PTH ↓ |
| ▪ Thyroid (TSH) | ▪ SPEP, UPEP |
| ▪ Celiac Panel | |
| ▪ Testosterone (Men) | |
| ▪ 24 Hour Urine Calcium, Creatinine | |

Camacho P. Endocrine Pract 2016; 22 (Suppl 4):1-42.

Osteoporosis Treatment

Who Should be Offered Treatment?

All Patients with Osteoporosis

- Fragility Fracture
- T-Score < -2.5 (any site)
- FRAX 10 Year Risk Criteria


Camacho P. Endocrine Pract 2016; 22 (Suppl 4):1-42.
Black DM, Rosen CJ. N Engl J Med 2016; 374:254-62.

Fall Prevention




Prevents Fractures
May be Most Effective Measure in the Elderly

Exercise



Aerobic




Resistance

Builds: Bone and Muscle
Improves: Balance

Calcium Nutrition

Milk
300 mg / 8 oz




Yogurt
300 mg / Cup

Cheese
300 mg / Oz


Dairy Products
Calcium Phosphate

If Dairy Intake Inadequate: Add Calcium Supplements
Total Calcium Intake Goal: 1000-1500 mg/day

Vitamin D Nutrition



Vitamin D



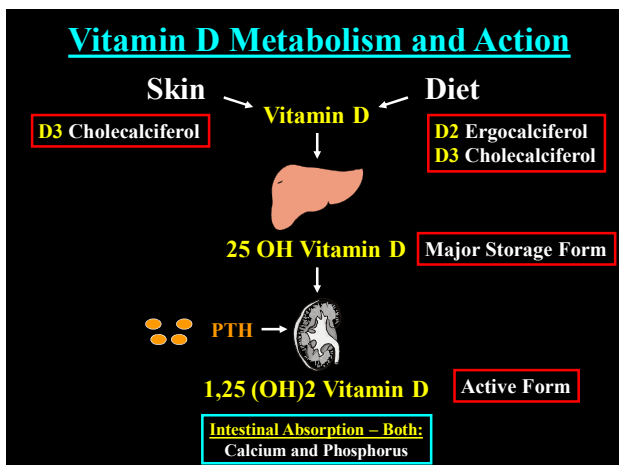
Sunlight

Fatty Fish

Dairy

Supplements

Vitamin D Supplements: Usually Needed
Total Vitamin D Intake Goal: 1000 Units/day



Vitamin D Deficiency

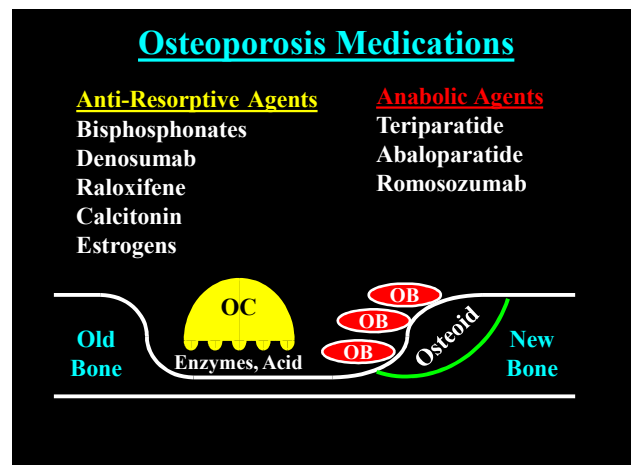
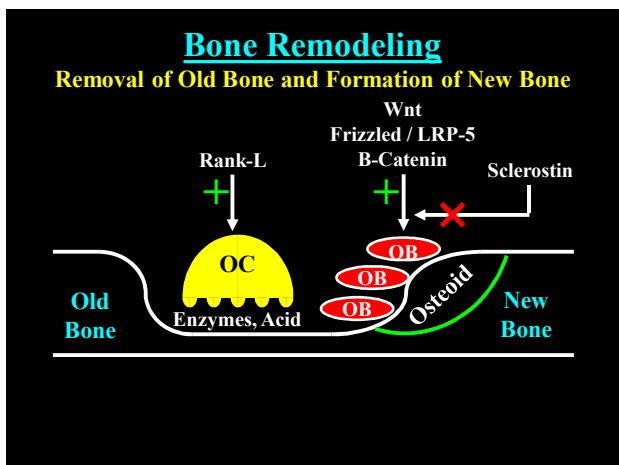
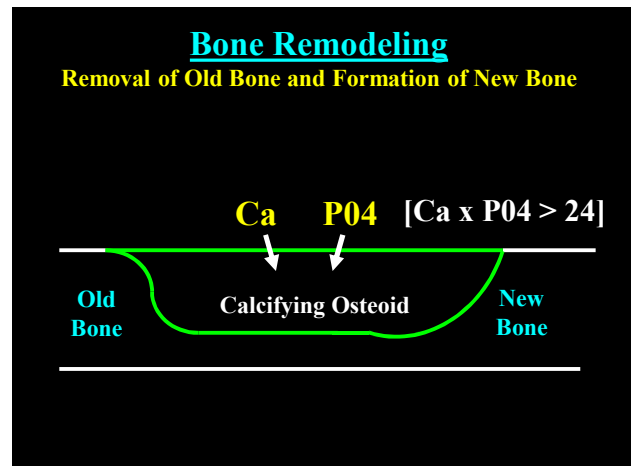
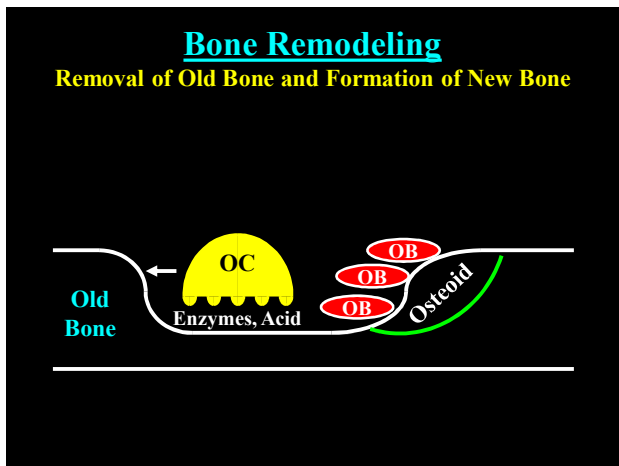
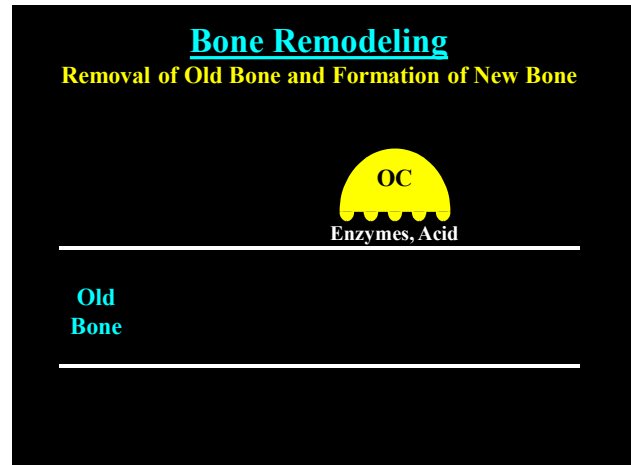
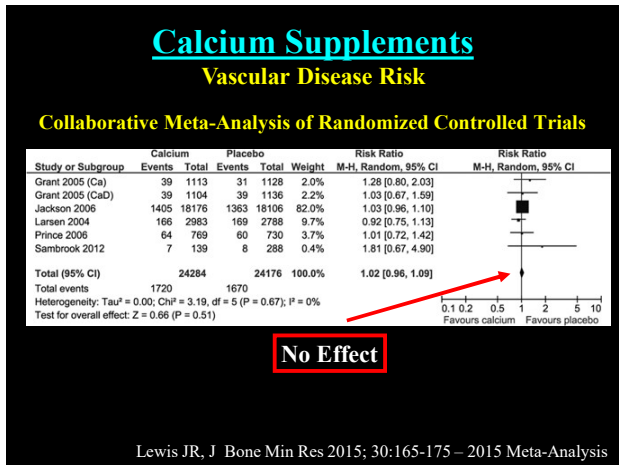
Replacement

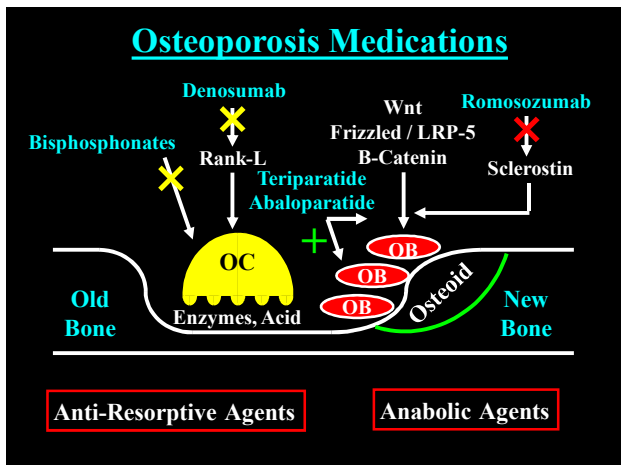
25 OH Vit D	Treatment
▪ < 10 ng/ml	50,000 U D2 BIW x 3 months
▪ 10-20 ng/ml	50,000 U D2 QW x 3 months
▪ 20-30 ng/ml	2,000 U D3 QD x 3 months

Maintenance

- **Optimal Intake:** 1,000 U QD
- **Safe Intake:** 2,000-4,000 U QD

Dawson Hughes B, Am J Clin Nutr 2004; 80:1763-6S





Osteoporosis Medications

Fracture Reduction

Vertebral Fractures	RR	Hip Fractures	RR
Alendronate	0.57	Alendronate	0.61
Risedronate	0.61	Risedronate	0.73
Ibandronate	0.67	Zoledronic Acid	0.60
Zoledronic Acid	0.38	Denosumab	0.56
Denosumab	0.32	Romosozumab	0.44
Teriparatide	0.27		
Abaloparatide	0.14		
Romosozumab	0.33		
Calcitonin	0.65		
Raloxifene	0.59		
Estrogens	0.65		

RR: compared with placebo

Barriounevo P. J Clin Endocrinol Metab 2019; 104:1623-30.
Eastell R. J Clin Endocrinol Metab 2019; 104:1595-1622.
Shoback D. J Clin Endocrinol Metab 2020; 105:587-594.

Osteoporosis Medications

Combination Therapy

Anabolic	Anti-Resorptive	Outcome
Teriparatide	+ Alendronate	No Synergy
Teriparatide	+ Zoledronic Acid	BMD Synergy
Teriparatide	+ Denosumab	BMD Synergy

Combination Therapy Not Recommended Yet

Sequential Therapy Is Recommended

Cosman F. J Bone Min Res 2012; 26:503-11
Leder B. J Clin Endocrinol Metab 2014; 99:1694-1700
Camacho P. Endocrine Pract 2016; 22 (Suppl 4):1-42.

Osteoporosis Treatment Decisions

Non-Fracture Patient

	Normal	Osteopenia	Osteoporosis
T-score	-1.0	-2.5	-3.0
Calcium Vitamin D Exercise	FRAX ≥ 3% Hip Fx, or ≥ 20% Major Fx		Bisphosphonates Denosumab Teriparatide Abaloparatide Romosozumab
	Fracture Patients Bisphosphonates Denosumab Teriparatide Abaloparatide Romosozumab	Optimize Non-Pharmacologic Rx Calcium: 1000-1500 mg daily Vitamin D: 1000 units daily Exercise: Aerobic and Resistance Fall Prevention	

Case

A 67 y.o. woman recently sustained painful vertebral fractures at T10 and T11.

PMH: None **Family Hx:** Hip Fracture - Mother

Calcium/Vitamin D: 1500 mg / 1000 U daily

Meds: None

Lab: Calcium 9.6 mg/dl, 25 Vitamin D 32 ng/ml, TSH 1.4 mU/L, Cr 1.1 mg/dl, SPEP normal

DEXA: Spine T-score -3.7, Fem Neck T-score -3.4

What treatment do you recommend for Osteoporosis?

- ### Osteoporosis Medications
- #### Risk Stratification
- Low / Moderate Risk**
- Oral Bisphosphonate (Alendronate, Risedronate)
 - Zoledronic Acid (Reclast)
 - Denosumab (Prolia)
- High Risk***
- Zoledronic Acid (Reclast)
 - Denosumab (Prolia)
 - Teriparatide (Forteo, Bonsity)
 - Abaloparatide (Tymlos)
 - Romosozumab (Evenity)
- High Risk*:** Old Age, Prior Fractures, Very Low BMD, High Fall Risk, Glucocorticoid Use

Osteonecrosis of the Jaw (ONJ)

Non-Healing Exposed Bone for ≥ 8 Weeks



FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zoledronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)

Ruggiero S, J Oral Maxillofac Surg 2004; 62:524-34

Osteonecrosis of the Jaw (ONJ)

Highest Risk

High Dose Anti-Resorptive Rx for Cancer

Periodontal Disease / Poor Oral Hygiene

Stop Anti-Resorptive Rx for 3 Months (Dental Work)

Reasonable - No Data for Efficacy

Anabolic Agents Are Not Associated with ONJ

Ruggiero S, J Oral Maxillofac Surg 2014; 72:1938
Khan AA, J Bone Min Res 2015; 30:3-23

Atypical Femur Fractures



Lenart B, N Engl J Med 2008;358:1304-6

Atypical Femur Fractures

- Femoral Shaft Fractures
- Non-Healing Stress Fractures
- Thigh Pain \rightarrow Often No Prior Trauma
- Prolonged Anti-Resorptive Rx (> 5 years)

Anabolic Agents Are Not Associated with AFF

Shane E, J Bone Min Res 2014; 29:1-23

Case

A 62 y.o. woman diagnosed with osteoporosis by BMD 7 years ago. No history of fragility fractures.

PMH: None **Family Hx:** Osteoporosis - MGM

Calcium/Vitamin D: 1200 mg / 600 U daily

Meds: Alendronate 70 mg weekly for 7 years

Lab: Calcium 9.4 mg/dl, 25 Vitamin D 48 ng/ml

BMD: Spine T-score -2.2, Fem Neck T-score -1.9

Significant \uparrow over 7 years, stable past 2 years

Do you recommend a bisphosphonate drug holiday?

Osteoporosis Medications

When Should Drug Holidays be Considered?

Bisphosphonates – Oral (daily, weekly, monthly)

- After 5 Years (Low / Moderate Risk Patients)
- After 6-10 Years (High Risk Patients)

Zoledronic Acid – IV (annually)

- After 3 Doses (Low / Moderate Risk Patients)
- After 6 Doses (High Risk Patients)

Denosumab – SQ (every 6 months)

Holiday Not Recommended. If stopped, must replace.

Teriparatide (2 yr) / Abaloparatide (2 yr) / Romosozumab (1 yr)

Holiday Not Recommended. If stopped, must replace.

Camacho P, Endocrine Pract 2016; 22 (Suppl 4):1-42.
Qaseem A, Ann Intern Med 2017; 166:818-39

Case

A 66 y.o. woman diagnosed with osteoporosis by BMD 11 years ago. No history of fragility fractures.

PMH: None **Family Hx:** Osteoporosis - MGM

Calcium/Vitamin D: 1200 mg / 600 U daily

Meds: Bisphosphonate drug holiday x 4 years.

Lab: Calcium 9.7 mg/dl, 25 Vitamin D 54 ng/ml

DEXA: Spine T-score -2.6, Fem Neck T-score -2.4
Significant ↓ during past 2 years (> LSC)

Do you recommend ending the bisphosphonate drug holiday?

Osteoporosis Medications

When Should Bisphosphonate Holidays End?

- Fragility Fracture Occurs
- BMD ↓ (> Least Significant Change)
- Bone Turnover Markers ↑ by 30% or into upper half of reference range)
 - Serum C-Telopeptide (CTX)
 - Urine N-Telopeptide (NTX)
 - Bone Specific Alkaline Phosphatase (BSAP)

Adapted from: Camacho P. Endocrine Pract 2016; 22 (Suppl 4):1-42.

Case

A 63 y.o. woman is being treated for osteoporosis. Recently fell and sustained a right wrist fracture.

PMH: Osteoporosis, Type 2 DM **Family Hx:** Negative

Calcium Intake: 1200 mg/d (diet plus supplements)

Meds: Alendronate (4 years), Metformin

PE: Ht 5'5" Wt 162 lb. Otherwise normal

Lab: Calcium 9.2 mg/dl, 25 Vitamin D 36 ng/ml

BMD:

	<u>T-score</u>	<u>Change (2 Year)</u>
Spine (L2-L4)	-2.6	-0.2 g/cm ² (< LSC)
Femoral Neck	-2.2	-0.1 g/cm ² (< LSC)

Is this considered a treatment failure?

Failure to Respond to Therapy

Definition

- Development of 2 or more fragility fractures
- BMD decrease > Least Significant Change

Lewiecki M, J Clin Densitom 2003; 6:307-14

Failure to Respond to Therapy

Causes and Management

- Poor compliance → **Education**
- Calcium / Vitamin D deficiency → **Correct**
- Co-morbid conditions → **Correct**
- Harmful medications → **Adjust**
- Wrong dose or dose interval → **Correct**
- Lack of efficacy → **Change Medication**

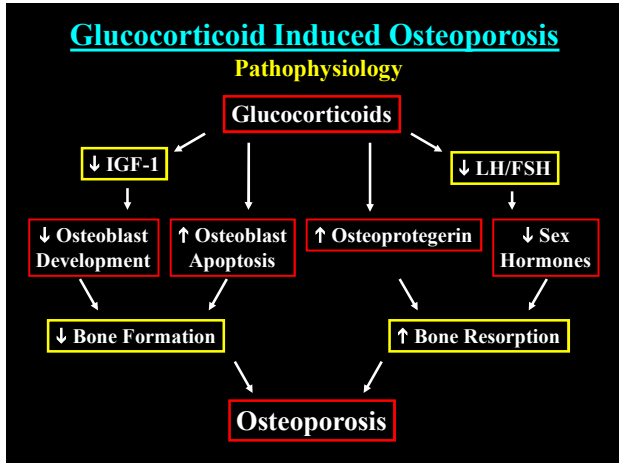
Lewiecki M, J Clin Densitom 2003; 6:307-14

Failure to Respond to Therapy

Change Medication

- Zoledronic Acid
- Denosumab
- Teriparatide
- Abaloparatide
- Romosozumab

Lewiecki M, J Clin Densitom 2003; 6:307-14



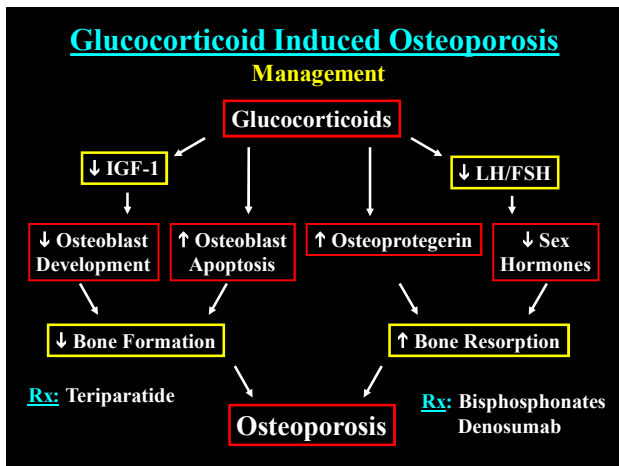
Glucocorticoid Induced Osteoporosis

Management

Non-Pharmacological Measures: All people

Medication: Prednisone ≥ 7 mg/day for ≥ 3 months

- Fragility fractures
- Postmenopausal women
- Premenopausal women and men with T score < -1.0



Chronic Kidney Disease

Stage 4, Stage 5

- Optimize Lifestyle (Calcium, Vitamin D, Exercise)
- Control Serum Phosphorus (reduce \uparrow PTH)
- Order Bone Specific Alkaline Phosphatase and PTH
 - Adynamic bone disease unlikely if \uparrow BSAP and PTH > 100
- Stage 4 CKD (eGFR 15-30)
 - Denosumab or low dose bisphosphonate
- Stage 5 CKD (eGFR < 15)
 - Low dose bisphosphonate

Case

A 68 year old woman complains of back pain. Spine films show 2 new vertebral fractures.

PMH: Hypertension **Meds:** Lisinopril

PE: BP 136/84 P 80 Ht 5'9" Wt 145 lb.

Normal otherwise

Lab: Ca 11.6 Phos 3.0 PTH 123 (nl: 10-65)

BMD: Spine T-score -2.8 Hip T-score -3.2

What is the cause of her vertebral fractures?

What is the most appropriate management?

Case

A 42 year old woman complains of weakness and thigh pain. Bowel habits normal. Wears a veil.

Meds: none **Cigarettes:** none **Etoh:** none

PE: Ht 5'8" Wt 135 lb. normal exam

Lab: Ca 7.4 Phos 2.4 Alk Phos 215

BMD: Spine T-score -2.5 Hip T-score -3.1

Serum PTH: 112 pg/ml (nl, 10-65)

Serum 25 Vitamin D: 5 ng/ml (nl, 30-100)

What is the cause of her pain, weakness and low BMD?

Why is her PTH elevated?

What is the most appropriate management?

Nutritional Vitamin D Deficiency
Laboratory

- ↓ Serum Calcium
- ↓ Serum Phosphate
- ↓ Serum 25 OH Vitamin D
- ↑ Serum PTH (2^o HPTH)
- ↑ Serum Alkaline Phosphatase
(suggests Osteomalacia)

Vitamin D Deficiency

- | <u>25 OH Vit D</u> | <u>Treatment</u> |
|--------------------|----------------------------|
| ▪ < 10 ng/ml | 50,000 U D2 BIW x 3 months |
| ▪ 10-20 ng/ml | 50,000 U D2 QW x 3 months |
| ▪ 20-30 ng/ml | 2,000 U D3 QD x 3 months |

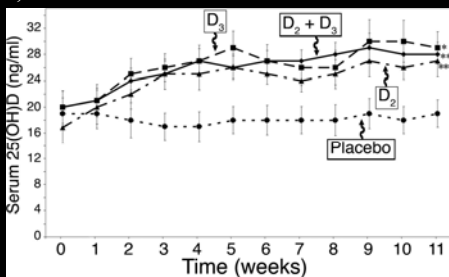
Maintenance

- **Optimal Intake:** 1,000 U QD
- **Safe Intake:** 2,000-4,000 U QD

Williams SE. Cleve Clin J Med 2022; 89:154-60.
Holick M, N Engl J Med 2007; 357:266-81
Dawson Hughes B, Am J Clin Nutr 2004; 80:1763-6S

Vitamin D Sources (D2 or D3)

68 Subjects: Age 18-84, End of Winter
RCT: 1,000 U D2 or D3 or 500 D2/ 500 D3 or Placebo QD



CLINICAL
ENDOCRINOLOGY
& METABOLISM

Holick MF, J Clin Endocrinol Metab 2008; 93:677-81

Case

A 54 y.o. woman is being treated for osteoporosis. She has recently sustained 2 vertebral fractures on therapy.

Calcium Intake: 1200 mg/d (diet plus supplements)
Meds: Risedronate (5 years), Levothyroxine 125 mcg
PE: Ht 5'5" Wt 162 lb. Tenderness over T-spine.
Lab: Ca 8.8 mg/dl, 25 D 8 ng/ml, PTH 101 pg/ml

Would you order additional tests?

Case

A 54 y.o. woman is being treated for osteoporosis. She has recently sustained 2 vertebral fractures on therapy.

Calcium Intake: 1200 mg/d (diet plus supplements)
Meds: Risedronate (5 years), Levothyroxine 125 mcg
PE: Ht 5'5" Wt 162 lb. Tenderness over T-spine.
Lab: Ca 8.8 mg/dl, 25 D 8 ng/ml, PTH 101 pg/ml

Celiac Panel: strongly positive

What do you recommend now?

Case

A 54 y.o. woman is being treated for osteoporosis. She has recently sustained 2 vertebral fractures on therapy.

Calcium Intake: 1200 mg/d (diet plus supplements)
Meds: Risedronate (5 years), Levothyroxine 125 mcg
PE: Ht 5'5" Wt 162 lb. Tenderness over T-spine.
Lab: Ca 8.8 mg/dl, 25 D 19 ng/ml, PTH 101 pg/ml

Celiac Panel: strongly positive

Gluten free diet recommended and explained.

She requests vitamin D intake through "natural" sources.

What do you advise?

Vitamin D Sources

Natural Sources	Vitamin D Content
Salmon	
Fresh, Wild (3.5 oz)	600-1000 U D3
Fresh, Farmed (3.5 oz)	100-250 U D3 or D2
Canned (3.5 oz)	100-600 U D3
Sardines, Canned (3.5 oz)	300 U D3
Mackerel, Canned (3.5 oz)	250 U D3
Tuna, Canned (3.5 oz)	230 U D3
Cod Liver Oil (1 tsp)	400-1000 U D3
Egg Yolk	20 U D3 or D2
Shiitake Mushrooms	
Fresh (3.5 oz)	100 U D2
Sun-dried (3.5 oz)	1600 U D2
Sunlight/UVB (0.5 MED*)	3000 U D3

*MED = Minimal Erythematous Dose
Arm + Leg exposure to sunlight for 5-10 minutes
Holick M, N Engl J Med 2007; 357:266-81

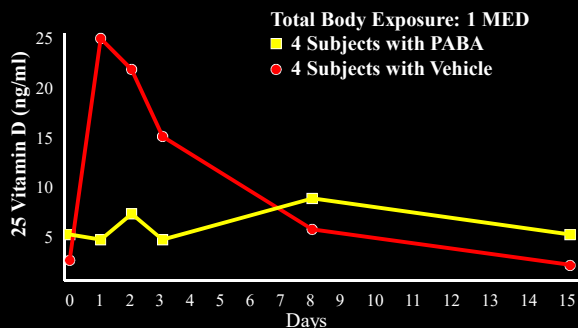
Vitamin D Sources

Fortified Foods	Vitamin D Content
Milk (fortified) (8 oz)	100 U D3
OJ (fortified) (8 oz)	100 U D3
Yogurt (fortified) (8 oz)	100 U D3
Infant Formulas (8 oz)	100 U D3
Cereals (fortified) (Serving)	100 U D3
Cheese (fortified) (3 oz)	100 U D3
Margarine (fortified) (3.5 oz)	430 U D3
Butter (fortified) (3.5 oz)	50 U D3

Holick M, N Engl J Med 2007; 357:266-81

Vitamin D Sources

Sunlight and Effects of Sunscreen



Matsouka L, J Clin Endocrinol Metab 1987; 64:1165-8

Vitamin D Sources

Sunlight and Various Effects

Cause	Vitamin D Synthesis
Sunscreen	
SP8	↓ 92.5%
SP15	↓ 99%
Pigmentation	↓ 99%
Aging (age 70)	↓ 75%
Season + Latitude	> 35 Latitude (Atlanta), minimal Vitamin D from Nov – Feb of each year

Holick M, N Engl J Med 2007; 357:266-81

Case

A 33 y.o. woman with malabsorption disorder.

PMH: Crohn's disease since age 12

Multiple bowel resections, Colectomy

Meds: Calcium 2400 mg/day, 4 Multivitamins,
Prednisone 10 mg/day, Pentasa

PE: Ht 5'2" Wt 102 lb. Otherwise normal

Lab: Calcium 8.6 mg/dl 25 Vitamin D < 5 ng/ml

BMD:

	T-score	Z-score
Spine (L2-L4)	-2.99	-2.25
Femoral Neck	-2.53	-1.87

How would you manage her vitamin D deficiency?

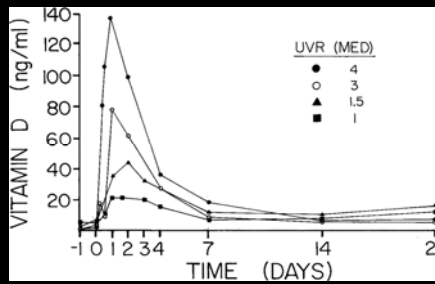
33 year old woman
with malabsorption

Vitamin D Dose	25 Vitamin D	Calcium	PTH
Multivitamins 4/day	< 5 ng/ml	8.6 mg/dl	
50,000 U BIW	22 ng/ml	9.4 mg/dl	30 pg/ml
50,000 U TIW	19 ng/ml	9.3 mg/dl	
50,000 U 5/Wk	20 ng/ml	8.6 mg/dl	
50,000 U QD	30 ng/ml	9.7 mg/dl	
50,000 U QD	5 ng/ml	8.1 mg/dl	132 pg/ml
50,000 U QD x 4 + 100,000 U QD x 3	12 ng/ml	9.1 mg/dl	49 pg/ml
100,000 U QD	11 ng/ml	9.2 mg/dl	45 pg/ml
100,000 U QD x 4 + 150,000 U QD x 3	26 ng/ml	9.1 mg/dl	
100,000 U QD x 4 + 150,000 U QD x 3	42 ng/ml	9.8 mg/dl	
100,000 U QD x 4 + 150,000 U QD x 3	30 ng/ml	9.3 mg/dl	

Vitamin D Synthesis in the Skin

Effects of UV Light (Sunlamp)

3 Subjects: Sunlamp (Wavelength 280-315 nm)
Whole Body : 1-4 Minimal Erythematous Dose (MED)



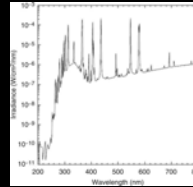
THE NEW ENGLAND JOURNAL OF MEDICINE

Adams JS, N Engl J Med 1982; 722-5

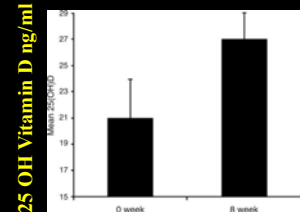
Therapy of Vitamin D Deficiency

UV Light in Subjects with Malabsorption

Short Bowel Syndrome (N = 2), Cystic Fibrosis (N = 5)
UV Light Exposure for 6 minutes twice weekly for 8 weeks (Portable UV Lamp)



UV Spectrum Output of Sperti Del Sol Sunlamp



Chandra P, Photoderm Photoimmunol Photomed 2007; 23:179-85

Therapy of Vitamin D Deficiency

Malabsorption

Malabsorption	Prevention and Maintenance
Oral Vitamin D	D2 (Ergocalciferol Rx) 50,000 U QW, QOD, QD or Higher as Needed
Sunlight / UVB Device	280-315 nm Wavelength

Holick M, N Engl J Med 2007; 357:266-81

Therapy of Vitamin D Deficiency

IM Vitamin D Injection

Injectable Vitamin D given under the supervision of health care professional.

Single-day dosing may be 15,000 micrograms (600,000 IU) of vitamin D.

Mayo Clinic Website

<http://www.zalmo.com/vitamins.html>

Summary of Osteoporosis Management

- **Diagnosis:** Fragility Fracture, T-score ≤ -2.5 , or FRAX Risk Criteria
- **Evaluation:** Search for cause of secondary bone loss
- **Treatment:** All patients with diagnosis of osteoporosis
- **Lifestyle Measures:** Calcium + Vitamin D Nutrition, Exercise and Fall Prevention
- **Medications:** Anti-Resorptive or Anabolic Drugs to Reduce Fractures

Thank You

