

Osteoporosis and Other Metabolic Bone Diseases

John P. Bilezikian, M.D. PhD (hon)

Silberberg Professor of Medicine

Vice-Chair for International Education and Research

Chief, Emeritus, Division of Endocrinology

Director, Emeritus, Metabolic Bone Diseases Unit

Vagelos College of Physicians and Surgeons

Columbia University, New York, NY

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John P. Bilezikian, MD, PhD (hon)

Disclosures:

John Bilezikian, M.D., faculty for this educational activity, is a consultant for Abiogen, Amgen, Amolyt, Ascendis, NovoNordisk, and Takeda Pharmaceuticals. He is also an adviser for Amgen, Amolyt, Ascendis and Radius Pharmaceuticals. He is also a speaker for Radius and Amgen. Dr. Bilezikian is also a member of the Data and Safety Monitoring Board for Regeneron. He has indicated that the presentation or discussion will not include off-label or unapproved product usage. Slides that do not have a specific attribution are those of the speaker.

3-24

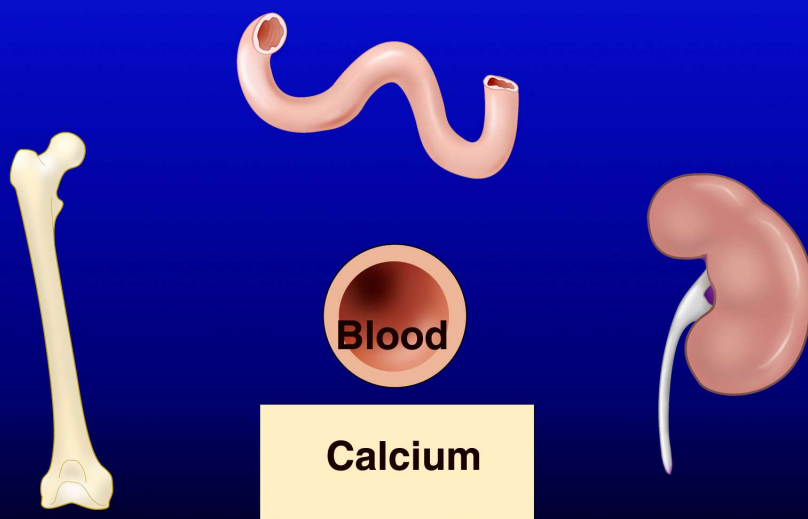
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Learning Objectives

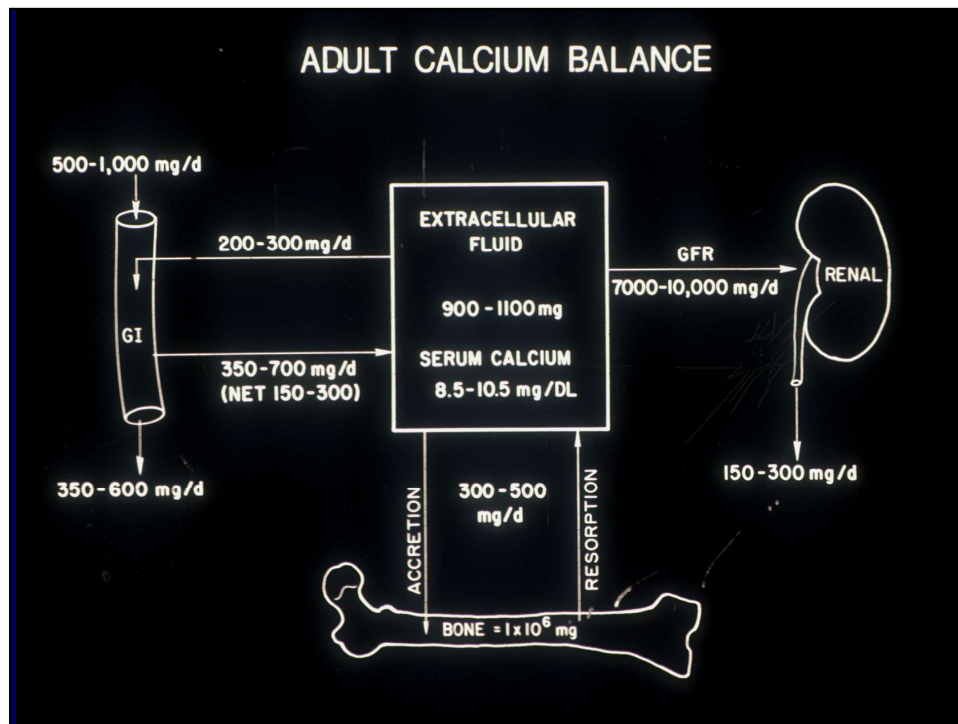
1. Describe the fundamentals of calcium metabolism.
2. Describe the pathophysiological mechanisms by which skeletal mass can be perturbed
3. Discuss the diagnosis, evaluation, and therapeutic concepts of major metabolic bone diseases such as osteoporosis and the parathyroid disorders.

3

Regulation of Serum Calcium



4



5

Two Major Calcium-Regulating Hormones

- **Parathyroid hormone**
- 1,25-dihydroxyvitamin D

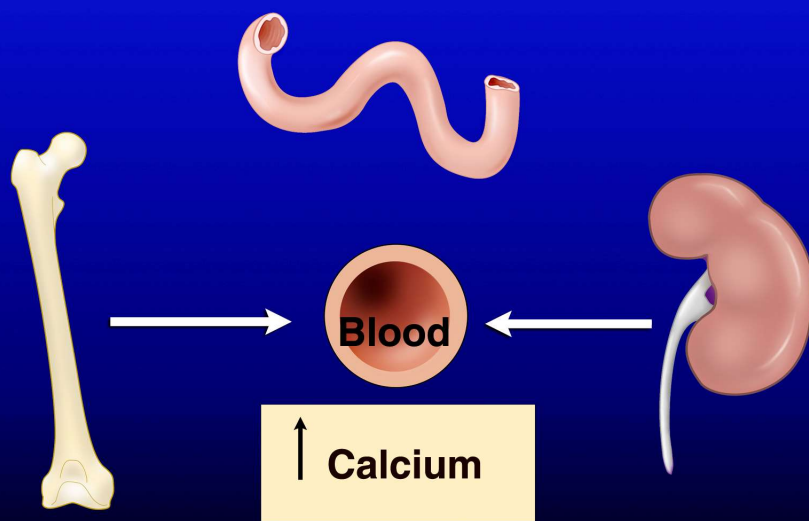
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Major Functions of Parathyroid Hormone

- Bone remodelling
- Regulation of serum calcium and phosphate
- Regulation of 1,25-dihydroxyvitamin D levels

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PTH: Effect on Serum Calcium

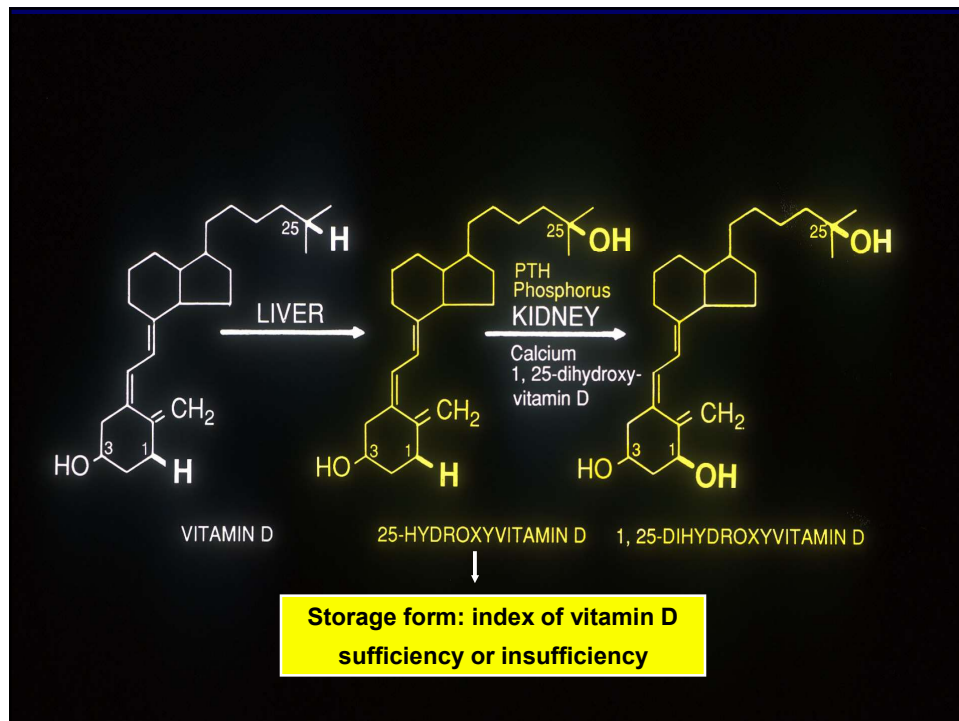


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Two Major Calcium-Regulating Hormones

- Parathyroid hormone
- 1,25-dihydroxyvitamin D

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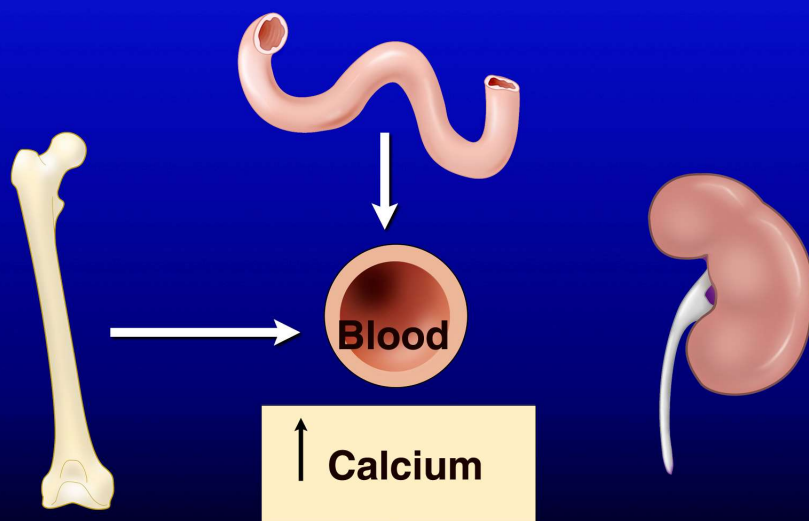
10

Major Functions of 1,25-dihydroxyvitamin D

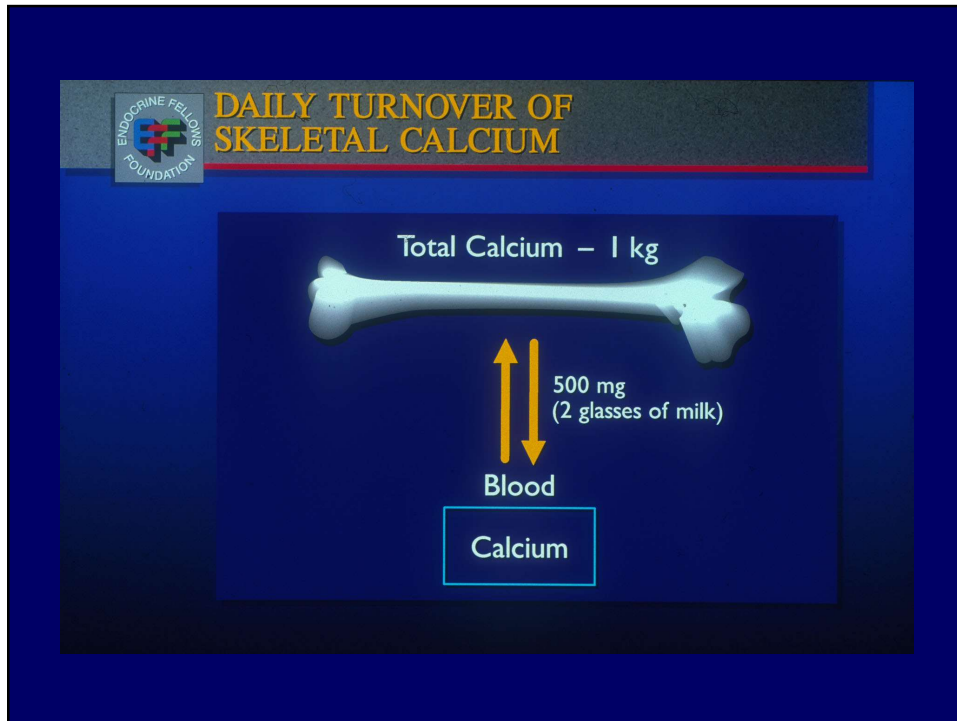
- GI absorption of calcium and phosphate
- Bone remodelling
- Regulation of parathyroid hormone

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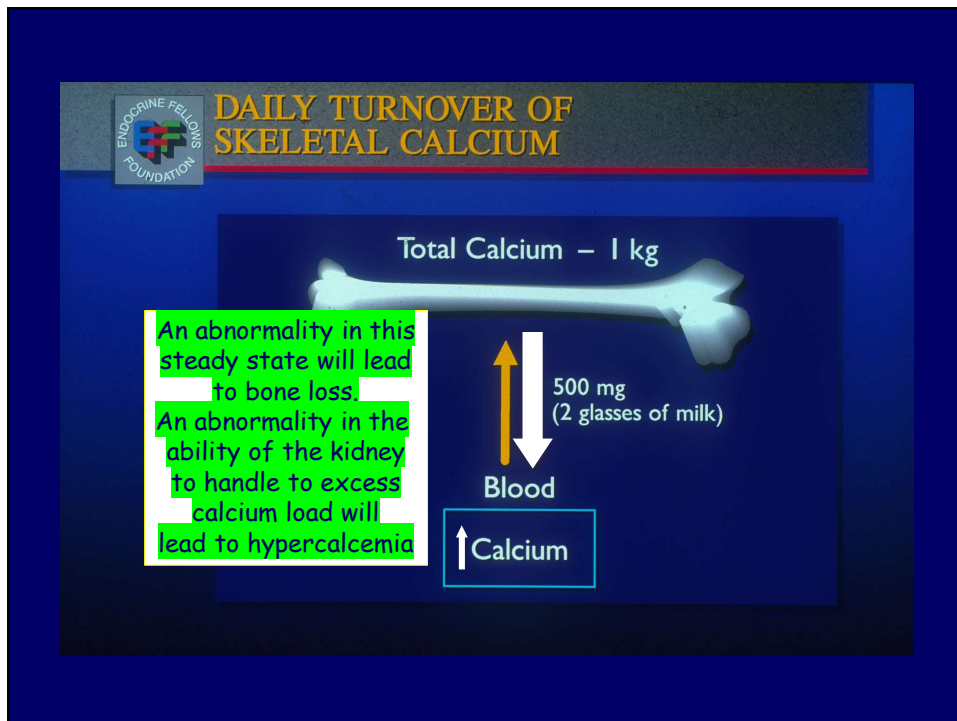
1,25(OH)₂D: Effect on Serum Calcium



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There are many causes of hypercalcemia

Mottaghzadeh Y, Bilezikian JP, Sellmeyer DE. Rare causes of hypercalcemia: 2021 update. J Clin Endocrinol Metab 106:3113-3128, 2021

What are the most common causes of hypercalcemia?

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CAUSES OF HYPERCALCEMIA*

- **Primary Hyperparathyroidism**
- **Malignancy**
- **Other endocrinopathy**
 - Hyperthyroidism
 - Pheochromocytoma
 - VIPoma
 - Adrenal insufficiency
- **Medications**
 - lithium
 - thiazide diuretics
 - thyroid hormone
 - Vitamin A
 - Vitamin D
- **Vitamin D**
 - Toxicity
 - CYP 24 A1 enzyme deficiency
 - Granulomatous disease
 - Tuberculosis
 - Sarcoidosis
 - Any other
- **Lymphoma**
- **FHH**
- **Immobilization**
- **Acute or chronic renal disease**

*Mottaghzadeh Y, Bilezikian JP, Sellmeyer DE. Rare causes of hypercalcemia: 2021 update. J Clin Endocrinol Metab 106:3113-3128, 2021 (adapted from)

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What are the two major causes of hypercalcemia?

| | % OF TOTAL |
|---|------------|
| Primary Hyperparathyroidism (PHPT) | 54 |
| Malignancy | 35 |
| All Other Causes (sarcoid, hyperthyroidism, vit D intoxication, etc.) | 6 |
| Unknown | 5 |

**The most common cause of hypercalcemia in a well-appearing outpatient is PHPT!!

**The most common cause of hypercalcemia in an ill-appearing patient is malignancy!!

Mundy et al NEJM 1984

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PRIMARY HYPERPARATHYROIDISM

- A common endocrine disorder characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more parathyroid glands.
- Primary Hyperparathyroidism, classically, is associated with hypercalcemia and elevated levels of parathyroid hormone.

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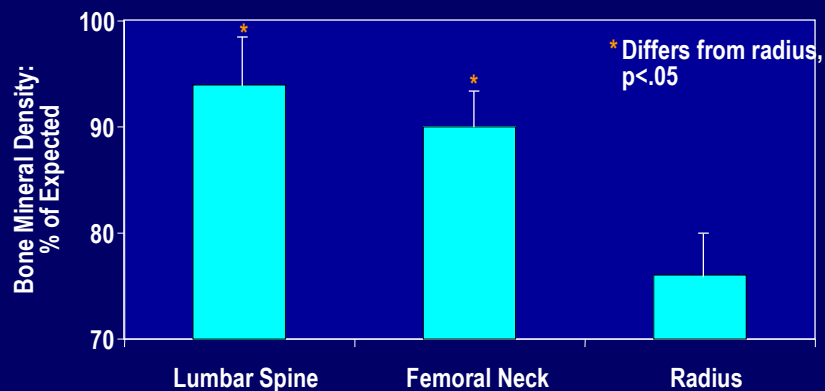
Baseline chemical and hormonal profile of asymptomatic primary hyperparathyroidism

| Index | Patients | nl range |
|--------------------------------------|----------|----------|
| • Calcium (mg/dl) | 10.7±0.1 | 8.4-10.2 |
| • Phosphorus (mg/dl) | 2.9±0.1 | 2.5-4.5 |
| • Alk Phos (IU/l) | 114±4 | <100 |
| • PTH (pg/ml) | 121±7 | 10-65 |
| • 25-OH Vit D (ng/ml) | 21±1 | 30-100 |
| • 1,25-OH ₂ Vit D (pg/ml) | 59±2 | 15-60 |
| • Urinary calcium (mg) | 248 ± 12 | 100-300 |
| • DPD (nmol/mmol Cr) | 17 ± 6 | 4-21 |

Silverberg, Bilezikian et al.

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BMD in Postmenopausal Women With Primary Hyperparathyroidism



Silverberg, Bilezikian et al.
JBMR, 1989

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Asymptomatic* Primary Hyperparathyroidism The dilemma:

- Who needs surgery?
- Who doesn't?

**All patients with symptomatic PHPT should undergo parathyroid surgery unless medically contraindicated*

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Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism (Bilezikian et al. JBMR, 2022)*

| Index | Guideline: any one of the following |
|------------------------------|--|
| Serum calcium (above normal) | > 1 mg/dL |
| Skeletal Involvement | A Fx by VFA or X-Ray; or DXA: T-Score \leq -2.5 at any site |
| Renal | Creatinine clearance or eGFR < 60 ml/min; or Stone or nephrocalcinosis by X-ray, CT, or ultrasound; or Urinary calcium (mg/day) >300 (men); >250 (women) |
| Age | < 50 years alone (without any aforementioned criteria) |

* Parathyroid surgery can also be performed if none of these guidelines is met with the concurrence of the patient and there are no contraindications.

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Approach to Patients with PHPT Followed Without Surgery

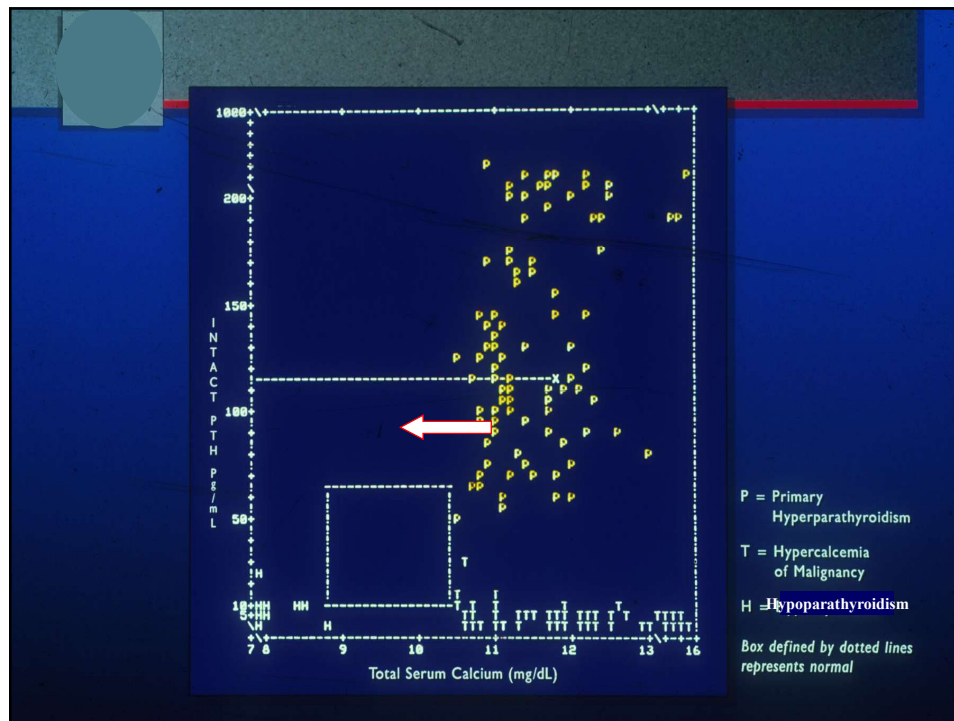
Non-Pharmacologic

- Dietary Calcium
- Hydration
- Mobilization
- Avoid thiazides & lithium if possible

Pharmacologic

- Estrogen
- SERMs
- Bisphosphonates
- Denosumab
- Calcimimetics

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Another Clinical Presentation of Primary Hyperparathyroidism

Normocalcemic primary hyperparathyroidism

*Silverberg SJ, Bilezikian JP et al. J Clin Endocrinol Metab 88:2003
Bilezikian et al. J Bone Miner Res 2022*

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Normocalcemic primary hyperparathyroidism: what must be ruled out?

- Vitamin D deficiency
 - 25-hydroxyvitamin D < 30 ng/mL
- Renal insufficiency
 - eGFR < 60 mL/min
- Medications
 - Thiazide diuretics
 - Lithium
- Hypercalciuria
- Gastrointestinal malabsorption
- Other metabolic bone diseases that could be associated with elevated PTH (e.g., Paget's disease)

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**Guidelines for Surgery in Normocalcemic Primary
Hyperparathyroidism
(Bilezikian et al. JBMR, 2022)**

| Index | Guideline: | NO CONCLUSIONS ABOUT GUIDELINES FOR SURGERY WERE REACHED IN NORMOCALCEMIC PHPT |
|---------------------------------|------------|---|
| Serum calcium (above normal) | N/A | |
| Skeletal Involvement | ? | |
| Renal | ? | |
| Age | ? | |

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Causes of Hypocalcemia

- **Hypoparathyroidism** (low or absent parathyroid hormone)
 - **After neck surgery, autoimmune, congenital**
 - infiltrative, hypomagnesemia
- **Secondary Hyperparathyroidism** (appropriate increase in PTH)
 - Vitamin D deficiency or resistance
 - Renal failure (↑ phosphate, ↓ calcitriol)
 - Gastrointestinal causes (malabsorption, celiac disease)
 - Pseudohypoparathyroidism

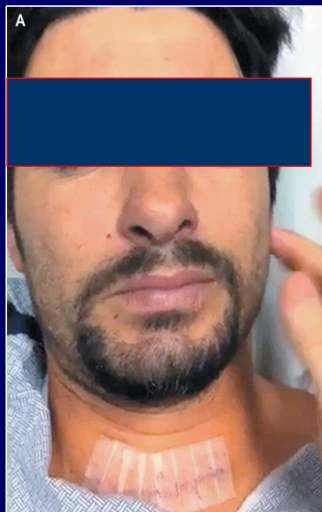
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Symptoms/Signs of Hypocalcemia

- Paresthesias (perioral and distal extremities)
- Tetany
- Muscle cramps
- Carpopedal spasm
- Seizures
- Chvostek and Trousseau's signs

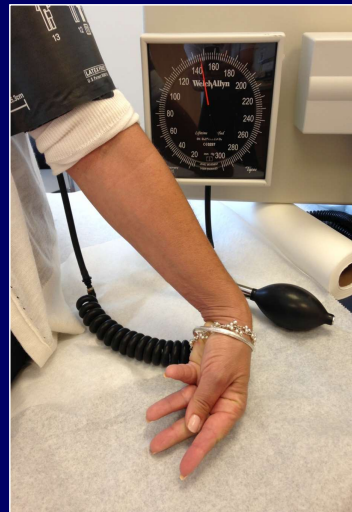
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Chvostek Sign



Jesus JE, Landry A. *N Engl J Med.* 2012;367:e15.

Trousseau Sign



Mannstadt MM, Mitchell DM. In: *The Parathyroids*. London: Academic Press; 2015:761-770.

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Treatment of hypocalcemic disorders

- Underlying disorder, if possible
- Calcium
- Vitamin D

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Treatment of hypoparathyroidism

- Calcium
- Active Vitamin D
- Parent Vitamin D
- Thiazide diuretics (for hypercalciuria)
- Parathyroid hormone
 - PTH(1-84) no longer available in the USA
 - “TransconPTH” FDA decision expected May, 2024
 - Phase 3 trial of another PTH formulation is ongoing

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OSTEOPOROSIS: A MAJOR HEALTH PROBLEM FOR BOTH MEN AND WOMEN



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Postmenopausal Osteoporosis

- 2.0 Million Fractures Annually
- 40-50% life time risk in a typical 50 year old Caucasian woman
- Fractures occur at 3 main sites:

| | |
|------------|-------|
| Vertebral: | 15.6% |
| Hip: | 17.5% |
| Forearm: | 16.0% |

Melton LJ, et al. *J Bone Miner Res* 1992;7:1005-10.
 Looker AC, et al. *J Bone Miner Res* 1997;12:1761-8.
 National Osteoporosis Foundation. 1998, 2002.

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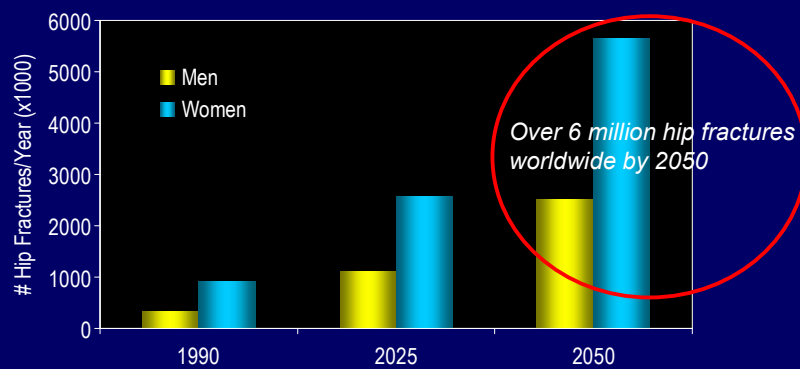
Osteoporosis

A GLOBAL PROBLEM

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Predicted Number of Hip Fractures Worldwide (Thousands)

Assuming 1% increase in fracture rate per year

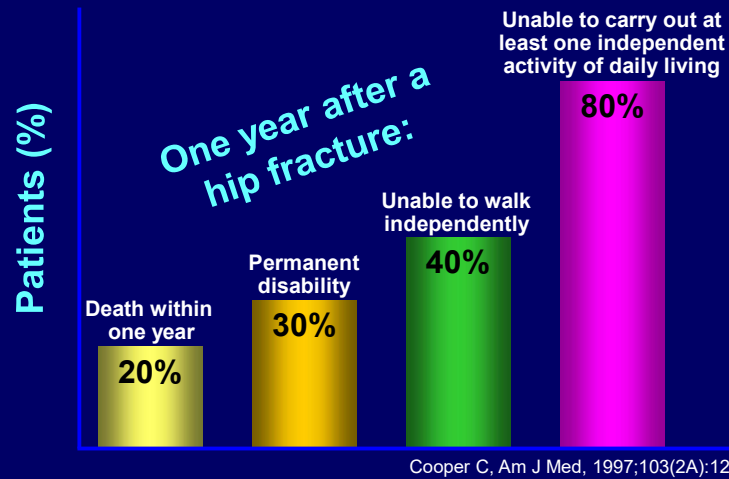


Socioeconomic impact of hip fractures will increase markedly, particularly in Asia.

Gullberg, *Osteoporosis Int.* 1997;7:407-413.

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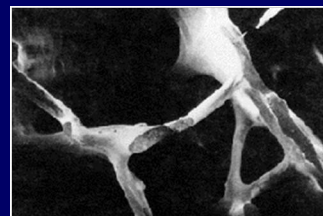
Morbidity After Hip Fractures



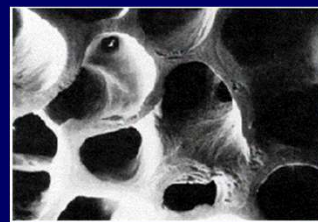
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Osteoporosis: Identifying the Problem

“ A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.”



Osteoporotic bone



Healthy bone

NIH Consensus Development Conference on Osteoporosis, 2000.

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DIAGNOSIS

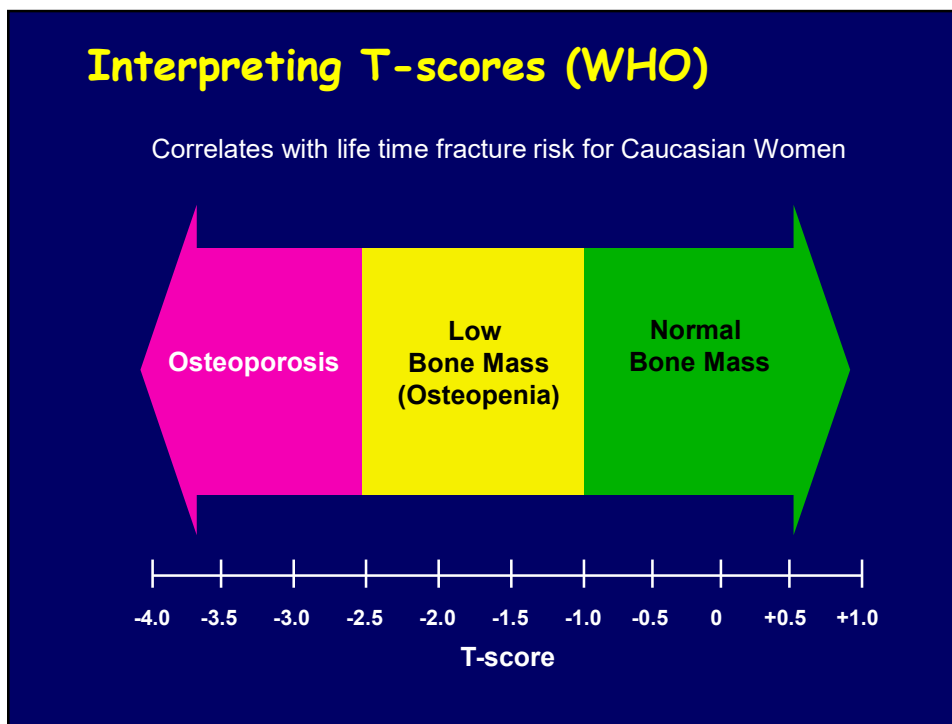
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Dual Energy X-ray Absorptiometry (DXA)

- Central DXA is the gold standard for diagnosis
- Measures the most important fracture sites (hip, spine, forearm)
- Can be used to monitor response to therapy



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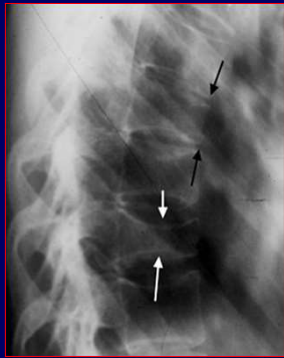
Who Should Have A Bone Density Test?

| | Women NOF¹/AAACE² | Men (³ISCD, ⁴Better Bones, ⁵TES) |
|--------------------|---|--|
| Age | >65 | >70 ³ |
| Fragility fracture | YES | YES |
| Starting steroids | YES | YES |
| Other risk factors | <65 if <ul style="list-style-type: none"> • Weight <127 lbs (58 kg) • Early menopause • Smoking • FH of fracture • Medical causes present | < 70 if <ul style="list-style-type: none"> • Low weight ? • Low T • Smoking • FH of fracture • Medical causes present |

¹ National Osteoporosis Foundation ² AAACE ³ ISCD, 2007 ⁴ Better Bones, 2007, ⁵ The Endocrine Society, 2012

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Don't Forget About Fractures



Osteoporosis can be diagnosed based on the presence or history of a low-trauma or fragility fracture



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CAN WE USE A FRAGILITY TO MAKE THE DIAGNOSIS OF OSTEOPOROSIS?

- A 60 year old woman trips on the sidewalk and breaks her hip. The fracture is not due to cancer or other disorder.
- Her T-score is -1.8.
- **Does she have osteoporosis or osteopenia?**

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FUNDAMENTAL PRINCIPLE:

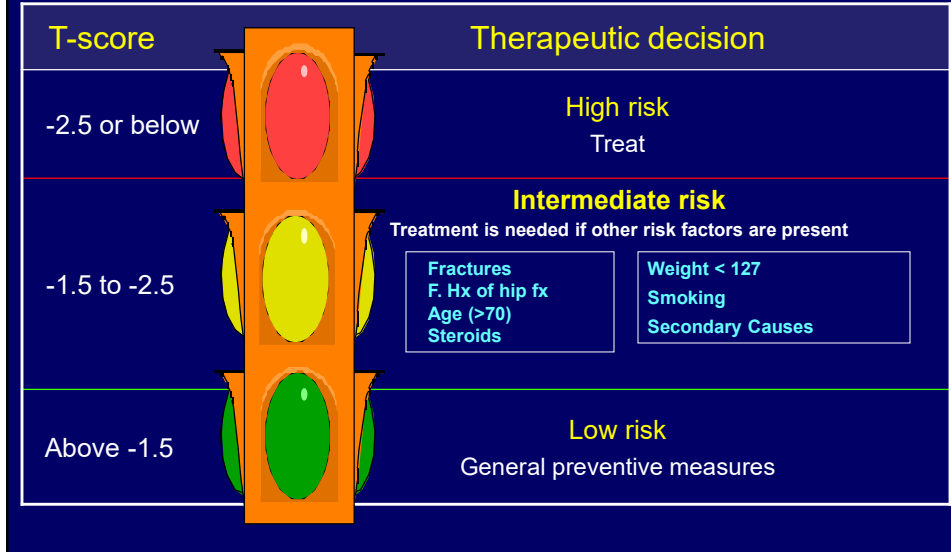
If a fragility fracture occurs in a postmenopausal woman, she has osteoporosis, even if the bone density T-score is not in the osteoporosis range.

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**Who else should be identified
as 'at risk'?**

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Identifying individuals with low bone mass who are at high risk for fragility fractures



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Quantifying Fracture Risk – The Frax Tool

WHO Fracture Risk Assessment Tool

[HOME](#) [CALCULATION TOOL](#) [PAPER CHARTS](#) [FAQ](#) [REFERENCES](#)

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Country : **US(Caucasian)** Name / ID : _____

[About the risk factors](#)

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age: Date of birth:

55 Y: M: D:

10. Secondary osteoporosis No Yes

11. Alcohol 3 more units per day No Yes

12. Femoral neck BMD

T-score -2.0

Clear Calculate

2. Sex Male Female

3. Weight (kg) 55

4. Height (cm) 156

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

BMI 22.6

The ten year probability of fracture with BMD

| | |
|--------------------|-----|
| Major osteoporotic | 10 |
| Hip fracture | 2.5 |

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NOF guidelines (2008) are based upon the Frax tool for estimating absolute fracture risk in clinical practice

Therapy indicated if 10-year risk of major fracture \geq 20% or \geq 3% for hip fracture

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Newest Version of FRAX is better, but still not perfect!

- Adjustments for
 - Lumbar spine BMD, if discrepant from femoral neck
 - Dose of Glucocorticoid, if > 7.5 mg/day,
 - Other contributors to bone strength (trabecular bone score)
- Rate of bone loss considered
- Secondary causes, besides RA, de-emphasized
- Long term risk not considered
- Risk of falling not taken into account

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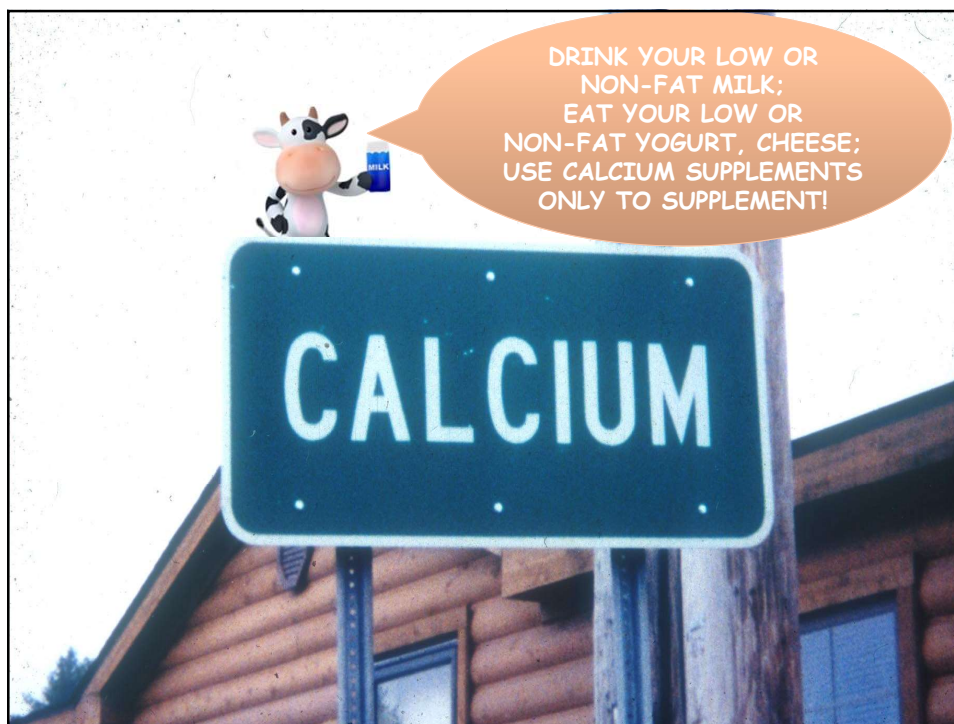


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Non-Pharmacologic Approaches to the Prevention or Treatment of Osteoporosis

- Calcium
- Vitamin D
- Appropriate exercise regimen
- Healthy life-style (no smoking; no excessive alcohol intake)
- Measures to prevent falls

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RDA for Calcium*
(Institute of Medicine Recommendations,
November, 2010)

- Men and women 19-50 yrs: 1000 mg/d
- Men 51-70: 1000 mg/d
- Men > 70 yrs: 1200 mg/d
- Women > 50 yrs: 1200 mg/d

Upper Limit: 2000 mg/d

**Not substantially different from recommendations of NIH
Consensus Development Panel on Optimal Calcium Intake
(Bilezikian et al, 1994)*

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The Institute Of Medicine Report (November 2010)

- Recommended daily intake: 600 IU (under 70 yrs); 800 IU (over 70 yrs old)
- Maximal daily intake: 4,000 IU
- *Aim for 25-hydroxyvitamin D level between 20 ng/mL and 50 ng/mL

*Some experts recommend 30 ng/mL as the better index of vitamin D adequacy

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EXERCISE

Childhood

- Stay active
- Stay active
- Stay active
- Stay active
- Stay active

Adulthood

- Walking
- Jogging
- Treadmill
- Weight training
- Tai Chi
- Swimming

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Efficacy Data Based upon Pivotal Clinical Trials Antiresorptives

| Agent | Vertebral | Nonvert | Hip |
|-----------------|-----------|---------|-----|
| Estrogen | + | + | + |
| Alendronate | + | + | + |
| Risedronate | + | + | + |
| Zoledronic acid | + | + | + |
| Ibandronate | + | - * | - |
| Denosumab | + | + | + |
| Raloxifene | + | - | - |
| Calcitonin | + | - | - |

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Efficacy Data Based upon Pivotal Clinical Trials Osteoanabolics

| Agent | Vertebral | Nonvert | Hip |
|---------------|-----------|---------|-----|
| Teriparatide | + | + | - |
| Abaloparatide | + | + | - |
| Romosozumab* | + | + | - |

*a dual action agent (anabolic and antiresorptive)

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Osteoporosis Therapy: Bisphosphonates

Effects

- Increases bone density in the spine by 5% to 8% and at the hip by 3% to 6% after 3 years
- Reduces incidence of vertebral fractures by 40% to 70%
- Alendronate, risedronate, and zoledronic acid reduce nonvertebral fractures (25% to 40%), including hip fractures (40% to 60%), in women with osteoporosis
- Ibandronate: overall, no effect observed on nonvertebral or hip fractures. In post-hoc analysis, nonvertebral fracture reduction was seen in high-risk subgroup (baseline femoral neck T-score less than -3.0)

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Prescribing information: <http://online.factsandcomparisons.com>.

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Adverse events associated with bisphosphonate use for osteoporosis

- Upper GI intolerance (oral agents)
- Acute Phase Reaction (more likely with IV agents)
- Musculoskeletal pain syndrome (rare)
- Atypical Fractures (very rare: after long term use)^{1,3-6}
- Osteonecrosis of the jaw²⁻⁶ (very, very rare)

¹Shane E et al. *J Bone Miner Res*, 2010, 2013

²Bilezikian JP *N Eng J Med*, 2006

³Khosla et al, *J Bone Mineral Res*, 2007

⁴Khosla, Bilezikian et al., *J Clin Endocrinol Metab* 2012

⁵Whitaker M et al, *N Eng J Med*, 2012

⁶Black DM and Rosen CJ, Postmenopausal Osteoporosis. *N Eng J Med*, 374:254-262, 2016

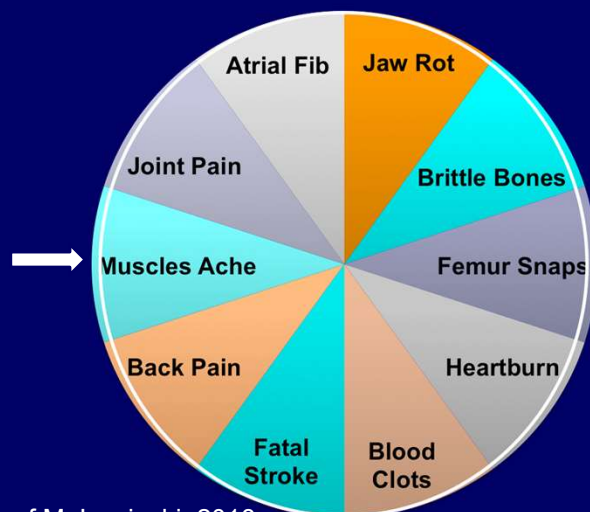
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The problem of perception with the bisphosphonates

- They cause the stomach to hurt (UGI distress)
- They cause the jaw to fall out (ONJ)
- They cause fractures (Atypical Femoral Fractures)
- They cause cancer (esophageal)
- All bisphosphonates are the same in regard to these AEs

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Osteoporosis Wheel of Fear*



*courtesy of M. Lewiecki, 2018

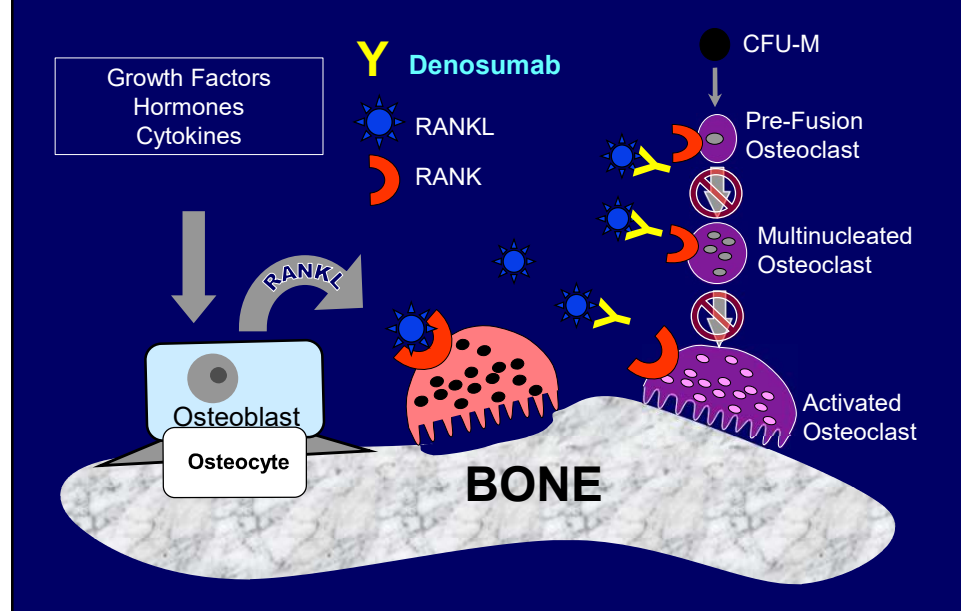
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The bisphosphonates: benefits and risks

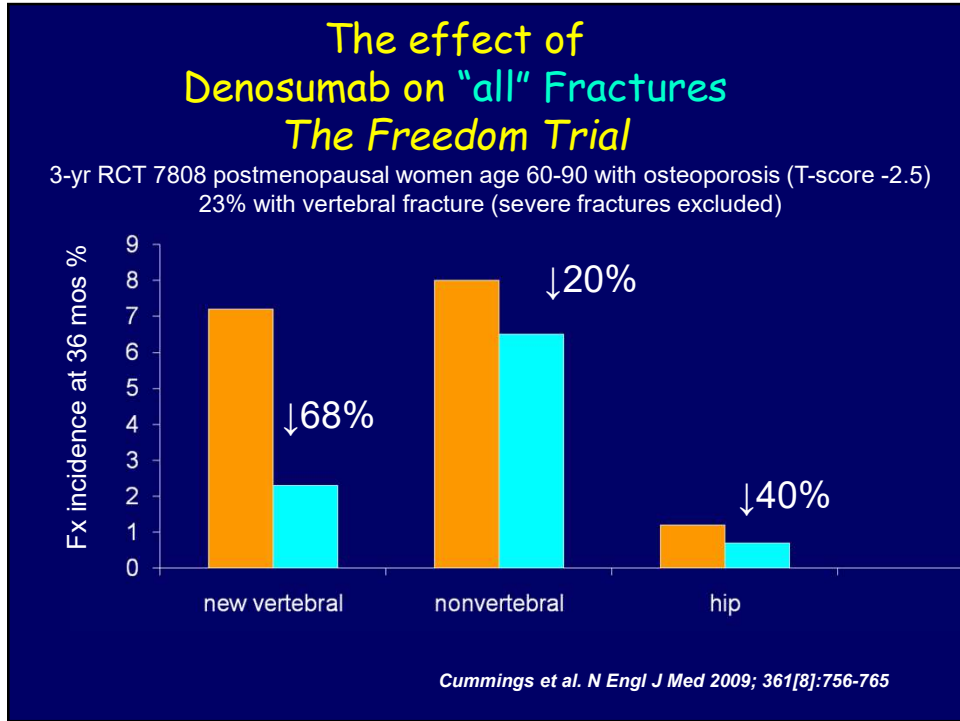
- The benefits of the bisphosphonates are clear: ALN, RIS, and ZOL all reduce fracture risk at all sites
- ONJ and AFF are rare events
- **Bisphosphonates cause more good than harm**

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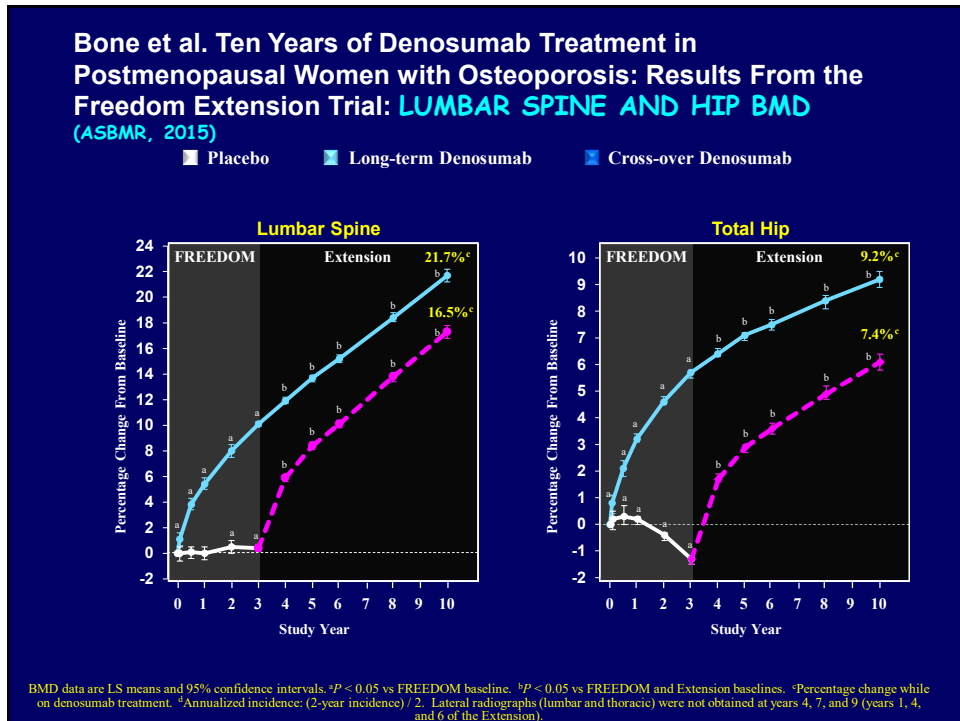
Denosumab, a human IgG antibody to RANKL, controls osteoclast differentiation, activation and survival



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Long-Term Effects of Denosumab

- Bone density continues to improve: over 10 yrs in the lumbar spine, > 20%
- This could mean a 2 unit improvement in T-score (e.g. -3.0 to -1.0!)
- What is our therapeutic target?
 - > -2.5?; > -2.0?; > -1.5?
 - What agent(s) can help to reach that goal?

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Example: Patient A

72 year-old woman with no known fractures, normal VFA, and mother with hip fracture, has FN T-score = -2.7

- **Current paradigm:** start treatment with generic oral bisphosphonate
- **Treatment to Target:** would you agree that we can achieve the target with a bisphosphonate?

Oral bisphosphonate likely to achieve treatment target

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Example: Patient B

81 year-old man with a prevalent VF (age unknown)
has FN T-score = -3.8

- **Current paradigm:** start treatment with generic oral bisphosphonate (as per payers!)
- **Treatment to Target:** It is highly unlikely that we can achieve a target with a bisphosphonate. In this case, denosumab is more likely to achieve this goal

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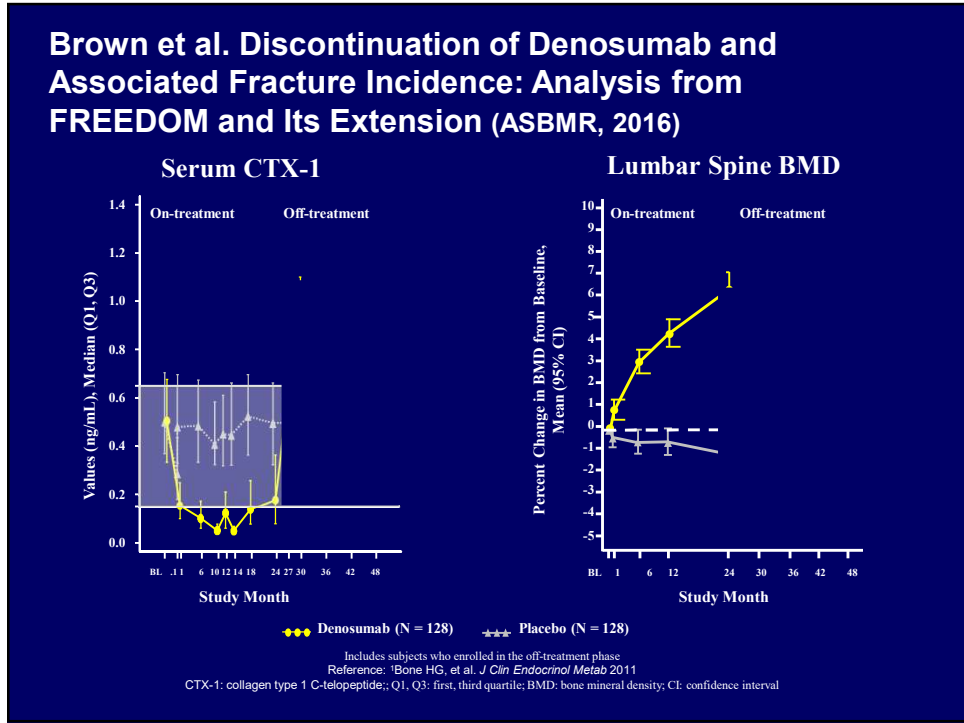


Denosumab

- When Denosumab is stopped.....

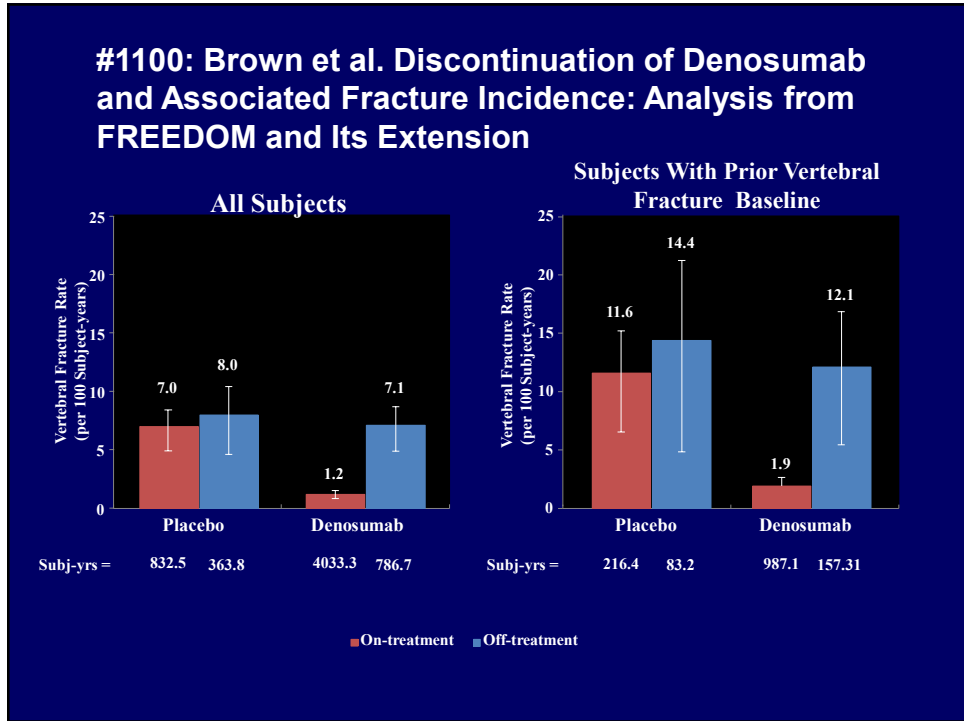
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Brown et al. Discontinuation of Denosumab and Associated Fracture Incidence: Analysis from FREEDOM and Its Extension (ASBMR, 2016)



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#1100: Brown et al. Discontinuation of Denosumab and Associated Fracture Incidence: Analysis from FREEDOM and Its Extension



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Fracture Risk after Discontinuation

Conclusions:

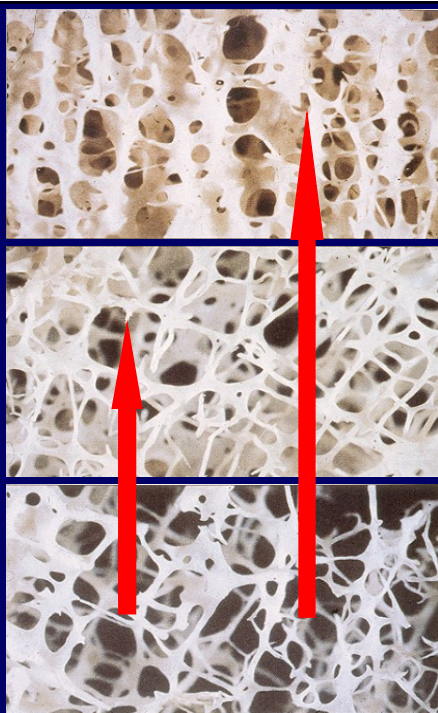
- Those with prior Vert Fx or who otherwise are at high risk should continue treatment
- Those who discontinue drug should be transitioned to another therapy

Prolia Package Insert, 2024

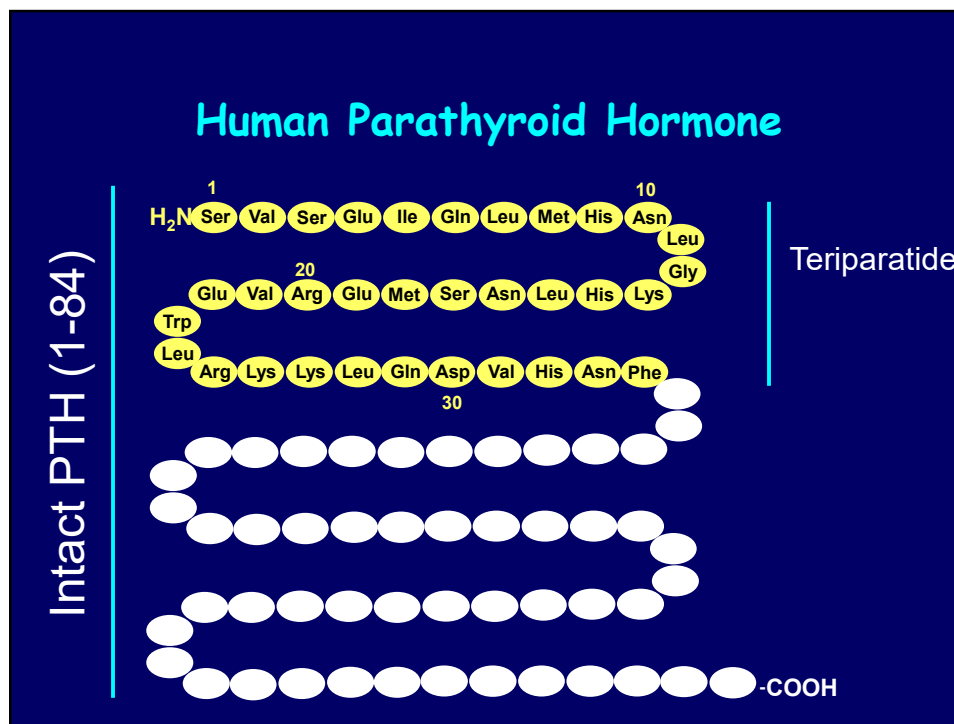
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What bisphosphonates
and other antiresorptives
don't do...

THE HOLY GRAIL?



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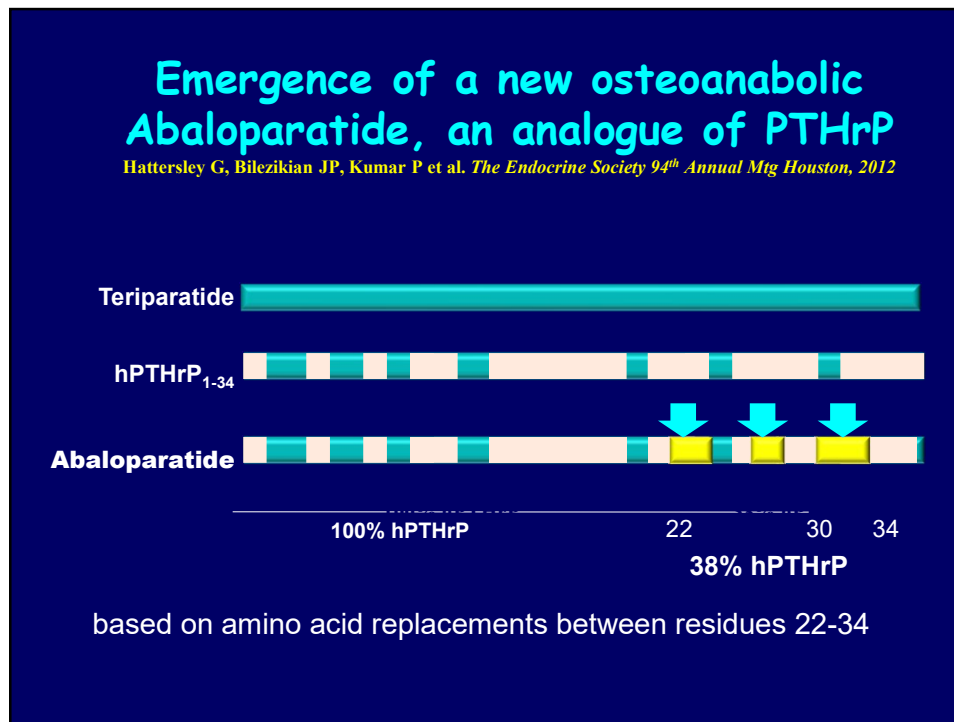


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Major Clinical Trials With Teriparatide; Safety Profile

- Reduction in vertebral (65%) and non-vertebral (53%) fractures (Neer et al. *N Eng J Med.* 2001)
- As effective in women with mild or severe previous fragility fractures (Gallagher et al. 2004)
- As effective in women with 1, 2 or more previous fragility fractures (Gallagher et al. 2004)
- Improved Microarchitecture
- Reduced back pain (McClung et al. 2005; Miller et al. 2006)
- Safety Profile: 15 years of surveillance: no osteosarcoma (Gilseman A et al. *J Bone Miner Res.* 2020): black box warning removed (FDA, 2020)

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Major Clinical Trials With Abaloparatide

- Reduction in vertebral (86%) and non-vertebral (43%) and clinical (45%) fractures (Miller et al. JAMA, 2016)
- Reduces all major osteoporotic fractures (70%) (Miller et al. JAMA, 2016)
- Persistent Fracture Reduction after transition to alendronate (Cosman et al. 2017)
- Well tolerated (Miller et al, 2017, Cosman et al, 2017)
- No boxed warning

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Summary: Teriparatide vs Abaloparatide

| Characteristics | Teriparatide | Abaloparatide |
|--|-------------------------------|---|
| Refrigeration | Yes | No |
| Daily Injectable | Yes | Yes |
| Dose | 20 mcg | 80 mcg |
| Limited period of approved therapy | no | Yes (but this restriction is likely to be removed soon) |
| 'Anabolic Window | Narrow | Wider |
| Adverse Event Profile | More hypercalcemia | More dizziness and palpitations |
| Safety Concerns Re Osteosarcoma in rats | Only under special conditions | Only under special conditions |

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CLINICAL TRIALS AND MECHANISMS OF THERAPEUTICS: ANTISCLEROSTIN ANTIBODY

Human Studies

- **Romsozumab** (approved by the FDA in April, 2019)

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Cosman F, Crittenden B, Adachi JD et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Eng J Med* 2016;375: 1532-1543

Design: Double-blinded, placebo-controlled, multinational study

Number: 7180

Inclusion: T-score, -2.5 to -3.5 TH or FN

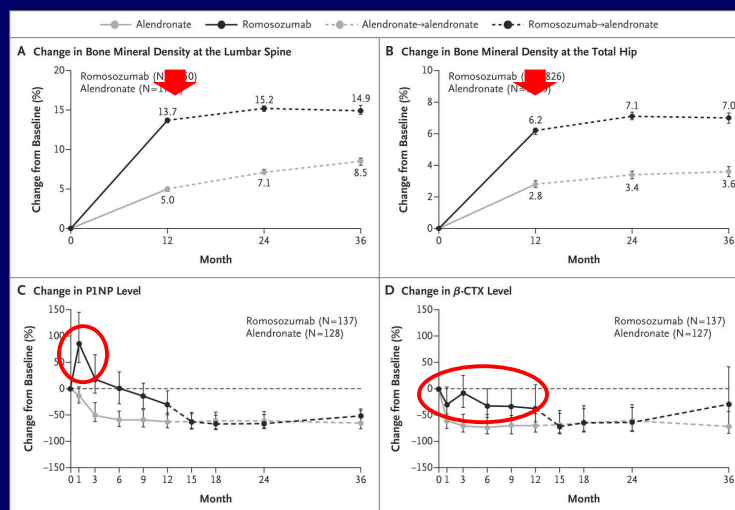
Drug: Romo 210 mg sc or placebo monthly x 12 months;
Followed by denosumab 60 mg sc x 12 months

Co-primary endpoints: cumulative incidence of new vertebral fractures at 12 and 24 months

Secondary endpoints: clinical (nonvertebral and symptomatic vertebral fractures) and nonvertebral fractures

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Percentage Change from Baseline in Bone Mineral Density and Levels of Bone-Turnover Markers.



Saag KG et al. *N Engl J Med* 2017;377:1417-1427.

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Cosman F, Crittenden B, Adachi JD et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Eng J Med 2016;375:1532-1543

RESULTS: **PRIMARY ENDPOINT:**

At 12 months: **New vertebral Fractures**

1.8% (PLB) vs 0.5% (Romo):
73% RR reduction (P <0.001)

At 24 months: **New Vertebral fractures**

New vertebral fractures:
2.5% (PLB to Dmab) vs 0.6% (Romo to Dmab):
75% RR reduction (< 0.001)

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Romsozumab: safety

- In the placebo-controlled trial, there was no difference in cardiovascular events (Cosman et al., 2016)
- In the alendronate comparator trial, there was a difference in cardiovascular events: Romo > ALN (Saag et al. 2017)
- FDA-Boxed warning about potential for cardiovascular effects of the drug in individuals at risk

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Conclusions (Take Home Messages)

- Calcium homeostasis is achieved by a balance of bone formation and bone resorption by diet and the calcium regulating hormones: parathyroid hormone and active vitamin D
- New guidelines for the management of Primary Hyperparathyroidism and Hypoparathyroidism are available
- Osteoporosis can be defined, evaluated, and treated in ways that should be accessible to general internists as well as specialists in metabolic bone diseases

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References

Walker MD, Shane E. Postmenopausal Osteoporosis 2023;23:1979-1991.

Bilezikian JP, Khan AA, Silverberg SJ, Fuleihan GEH, Marcocci C, Minisola S, Perrier N, Sitges-Serra A, Thakker RV, Guyatt G, Mannstadt M, Potts JT, Clarke BL, Brandi ML. Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. *J Bone Miner Res* 37:2293-2314, 2022. PMID 36245251

Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, Pasieka JL, Rejnmark L, Shoback DM, Potts JT, Guyatt G, Mannstadt M. Evaluation and Management of Hypoparathyroidism: Summary statement and Guidelines from the Second International Workshop. *J Bone Miner Res* 37:2568-2585, 2022 PMID 36054621

Motlaghzadeh Y, Bilezikian JP, Sellmeyer DE. Rare causes of hypercalcemia: 2021 update. *J Clin Endocrinol Metab* 106:3113-3128, 2021 PMID 34240162

Giustina A, Bouillon R, Binkley N, Sempos C, Adler RA, Bollerslev J, Dawson-Hughes B, Ebeling P, Feldman D, Heijboer A, Jones G, Kovacs CS, Lazaretti-Castro M, Lips P, Marcocci C, Minisola S, Napoli N, Rizzoli R, Scragg R, White JH, Formenti AM, Bilezikian JP. Controversies in Vitamin D: A statement from The 3rd International Conference. *JBMPlus* Dec; 4(12):e10417, 2020, PMID:PMC7811339

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Thank You!