



Parathyroid Hormone

Parathyroid hormone (PTH) is the peptide hormone that controls the minute-to-minute level of ionized calcium in the blood and extracellular fluids. PTH binds to cell surface receptors in bone and kidney, thereby triggering responses that increase blood calcium.

PTH also increases renal synthesis of $1,25(\text{OH})_2\text{D}_3$, the hormonally active form of vitamin D, which then acts on the intestine to augment absorption of dietary calcium, in addition to promoting calcium fluxes into blood from bone and kidney. The resulting increase in blood calcium (and in $1,25[\text{OH}]_2\text{D}_3$) feeds back on the parathyroid glands to decrease the secretion of PTH.

The parathyroid glands, bones, kidney, and gut are thus the crucial organs that participate in PTH-mediated calcium homeostasis.

Parathyroid Hormone

Parathyroid chief cells have three properties vital to their homeostatic function:

- 1) they rapidly secrete PTH in response to changes in blood calcium.**
- 2) they can synthesize, process, and store large amounts of PTH in a regulated manner.**
- 3) parathyroid cells replicate when chronically stimulated.**

These functional attributes allow for short-term, intermediate-term, and long-term adaptation, respectively, to changes in calcium availability.

Actions of Parathyroid Hormone on the Kidney

Stimulation of Calcium Reabsorption

Almost all of the calcium in the initial glomerular filtrate is reabsorbed by the renal tubules. Sixty-five percent or more is reabsorbed by the proximal convoluted and straight tubules via a passive, paracellular route.

Changes in the transepithelial voltage gradient, determined largely by the rate of sodium reabsorption, control the rate of calcium transport in the proximal tubule, and PTH does little to affect calcium flux in this region.

The remaining calcium is largely reabsorbed more distally—20% of the initial filtrate in the cortical thick ascending limb (cTAL) of Henle's loop and 10% in the distal convoluted and connecting tubules.

Actions of Parathyroid Hormone on Bone

The actions of PTH on bone are complicated because PTH acts on a number of cell types both directly and indirectly.

For years, the release of calcium from bone through stimulation of bone resorption has been considered to be the major action of PTH on bone.

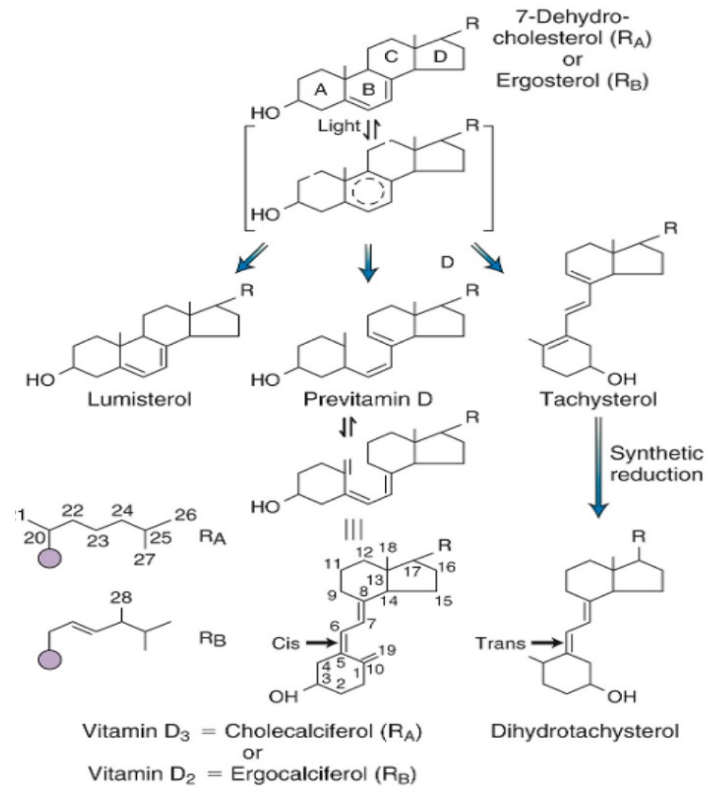
Vitamin D

Vitamin D is not a true vitamin, because nutritional supplementation is not required in humans who have adequate sun exposure. When exposed to ultraviolet irradiation, the cutaneous precursor of vitamin D, 7-dehydrocholesterol, undergoes photochemical cleavage of the carbon bond between carbons 9 and 10 of the steroid ring

Vitamin D

The resultant product, previtamin D, is thermally labile and over a period of 48 hours undergoes a temperature-dependent molecular rearrangement that results in the production of vitamin D. Alternatively, this thermally labile product can isomerize to two biologically inert products, luminosterol and tachysterol.

This alternative photoisomerization prevents production of excessive amounts of vitamin D with prolonged sun exposure.



Actions on the Parathyroid Gland

1,25(OH)₂D₃ has been shown to regulate gene transcription and cell proliferation in the parathyroids. The hormone also inhibits the proliferation of dispersed parathyroid cells in culture, although the relative contribution of calcium and 1,25(OH)₂D₃ in the regulation of parathyroid cell proliferation in vivo has not been established.

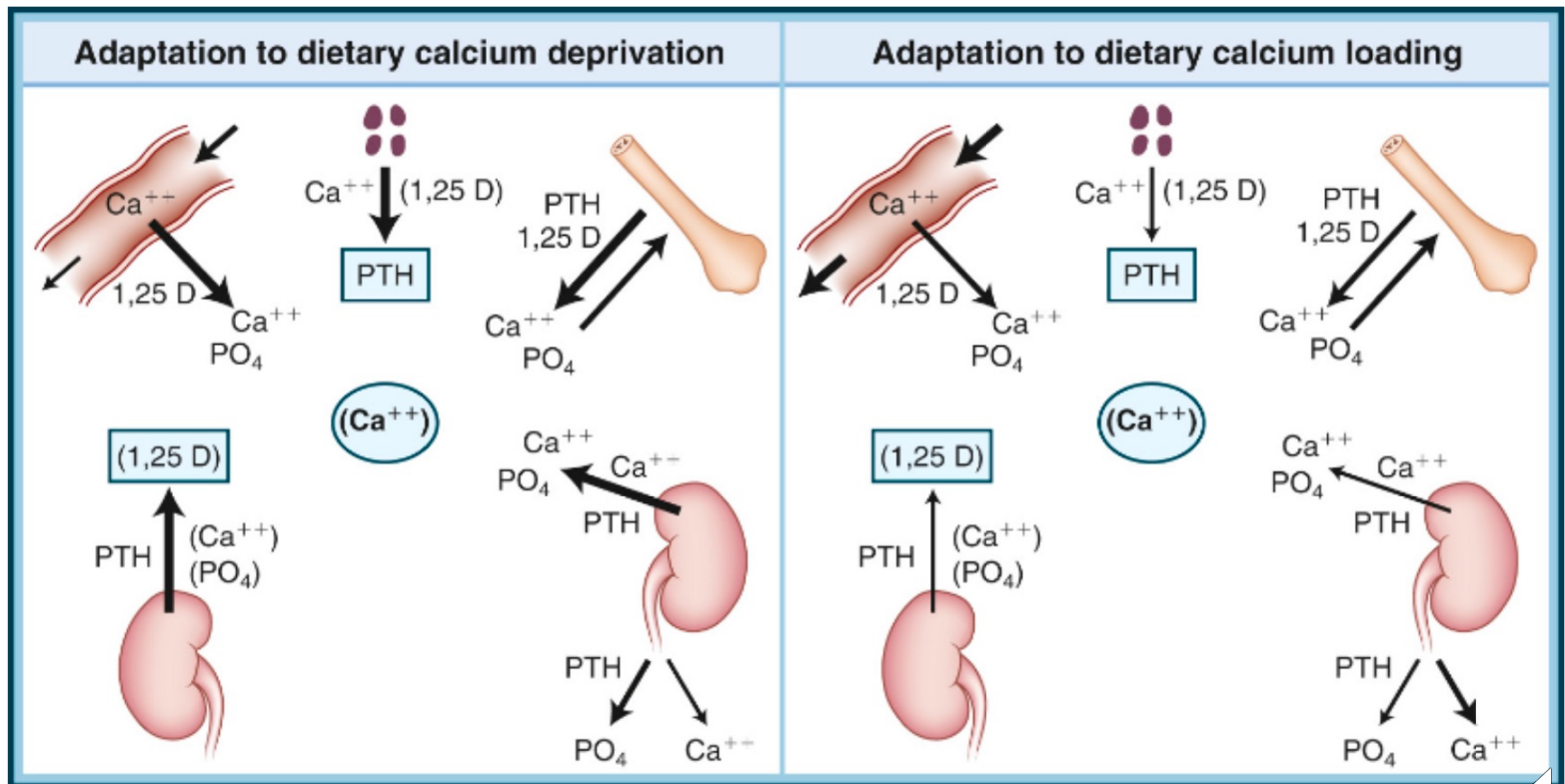
Actions on Bone

The effects of $1,25(\text{OH})_2\text{D}_3$ on bone are numerous. $1,25(\text{OH})_2\text{D}_3$ is a major transcriptional regulator of the two most abundant bone matrix proteins: it represses the synthesis of type I collagen and induces the synthesis of osteocalcin. $1,25(\text{OH})_2\text{D}_3$ promotes the differentiation of osteoclasts from monocyte-macrophage stem cell precursors in vitro and increases osteoclastic bone resorption in high doses in vivo by stimulating production of RANKL (also called osteoclast differentiating factor) by osteoblasts

Intestinal Calcium Absorption

Under normal dietary conditions, calcium intake is in the range of 700 to 900 mg daily. Approximately 30% to 35% of this calcium is absorbed; however, losses from intestinal secretion of calcium lead to a net daily uptake of approximately 200 mg.

Though vitamin D is the major hormonal determinant of intestinal calcium absorption, the bioavailability of mineral ions in the intestinal lumen may be affected by a number of local factors and dietary constituents. Absorption of calcium and magnesium is impaired by bile salt deficiency, unabsorbed free fatty acids in steatorrheic states, and high dietary content of fiber or phytate





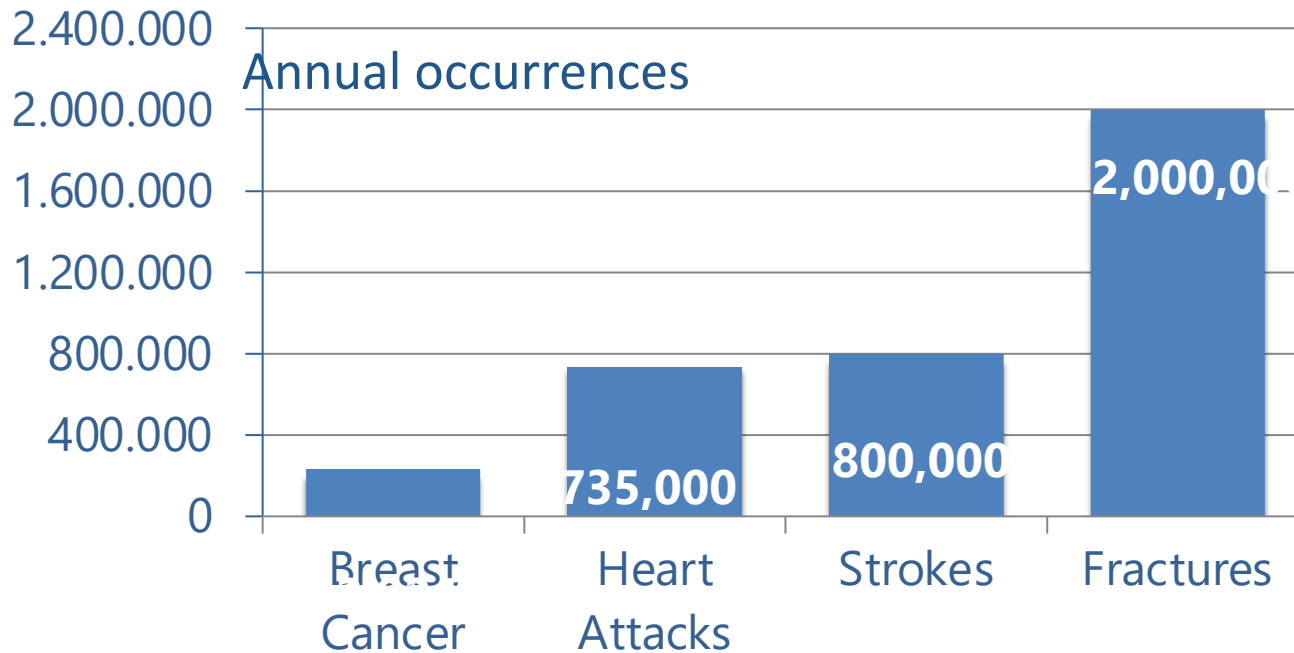
Osteoporosis is a Serious Problem

70%

of people over 65 with osteoporosis have never
been screened and don't know they have
osteoporosis



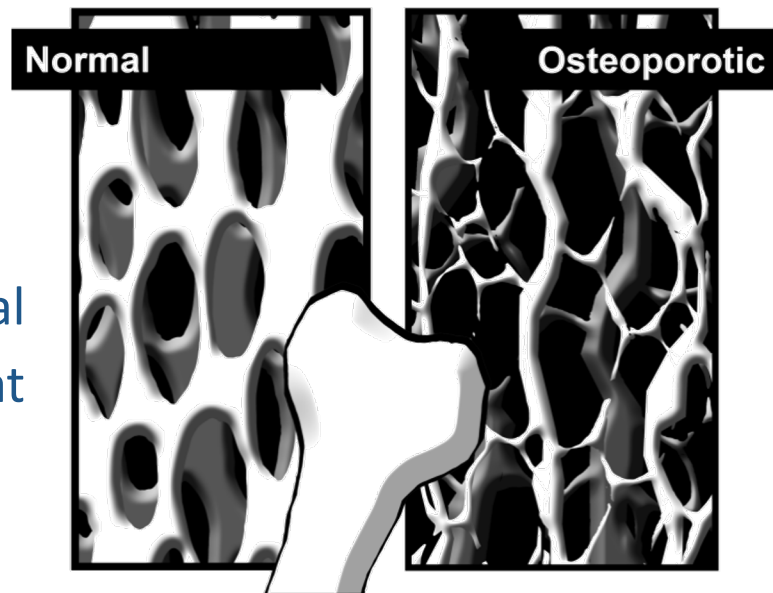
Compared to Other Health Issues



Centers for Disease Control & Prevention 2016
Centers for Disease Control & Prevention, 2015
Centers for Disease Control & Prevention, 2015
National Osteoporosis Foundation, 2015

Osteoporosis is a Disease

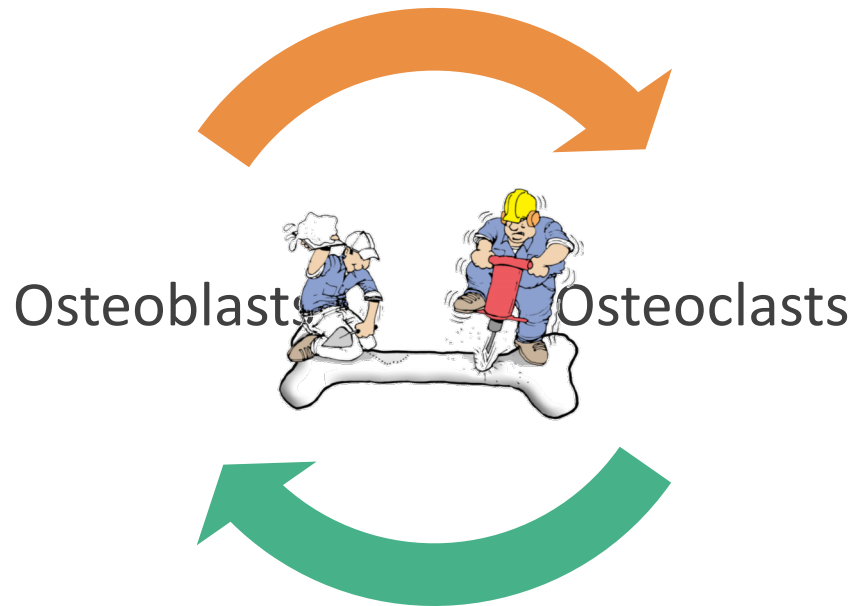
When the skeleton loses mineral density, the structure becomes thin and unable to take normal weight, leaving bones that break easily.



Defining Osteoporosis

- “systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk”
- True Definition: bone with lower density and higher fracture risk
- WHO: utilizes Bone Mineral Density as definition (T score <-2.5); surrogate marker

Bones Are Living Tissue

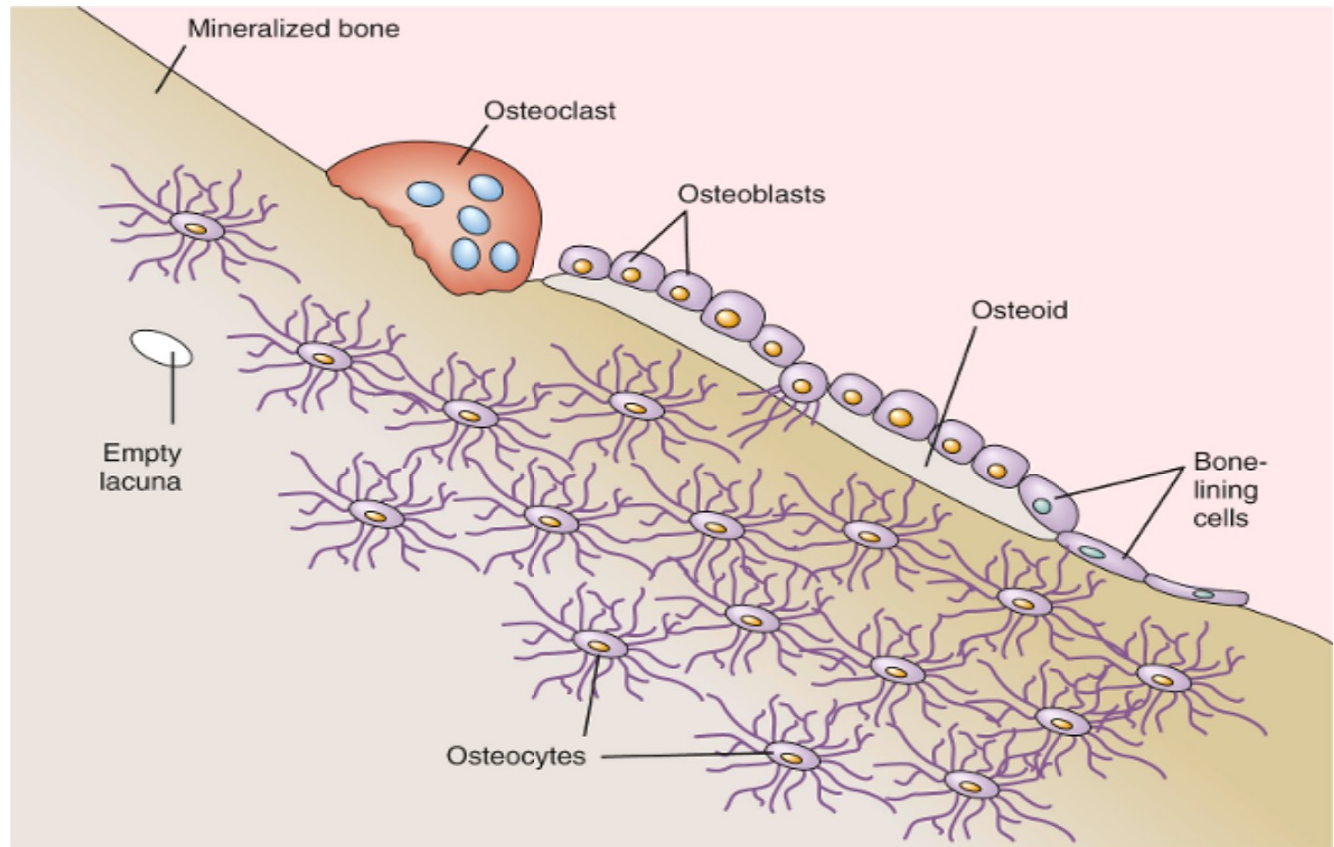


**Bone remodeling
means you have
the opportunity
to have
new bones
every
7-10 years!**

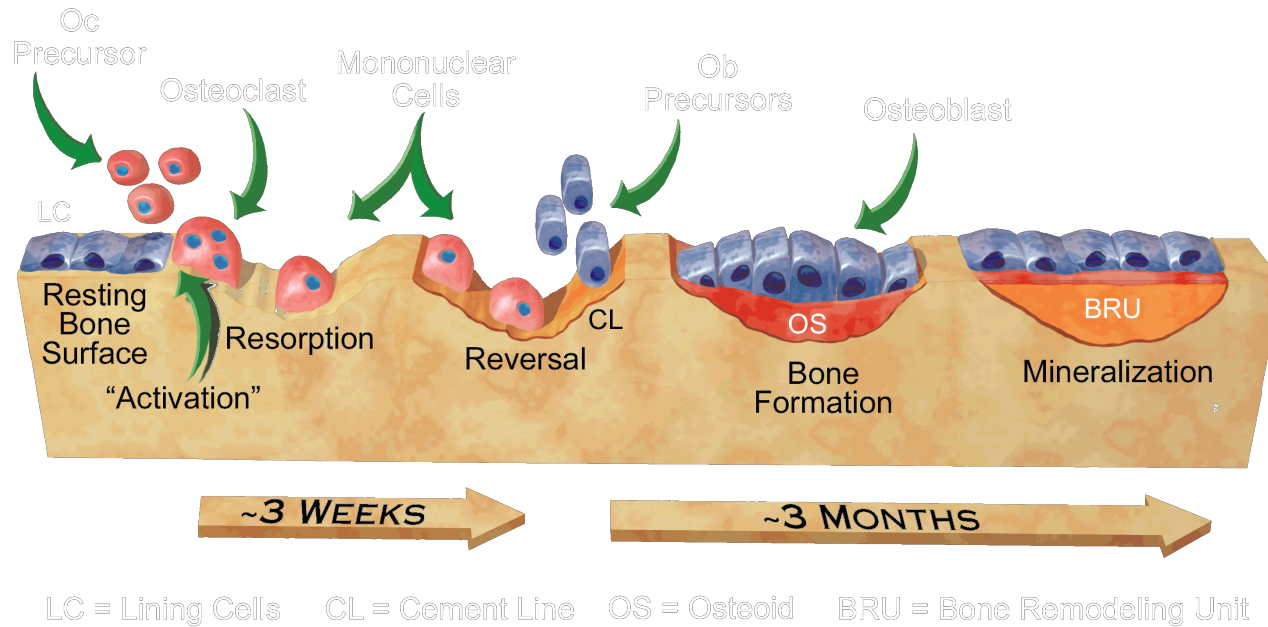
Osteoblasts- build new bone

Osteoclasts- remove old or damaged bone

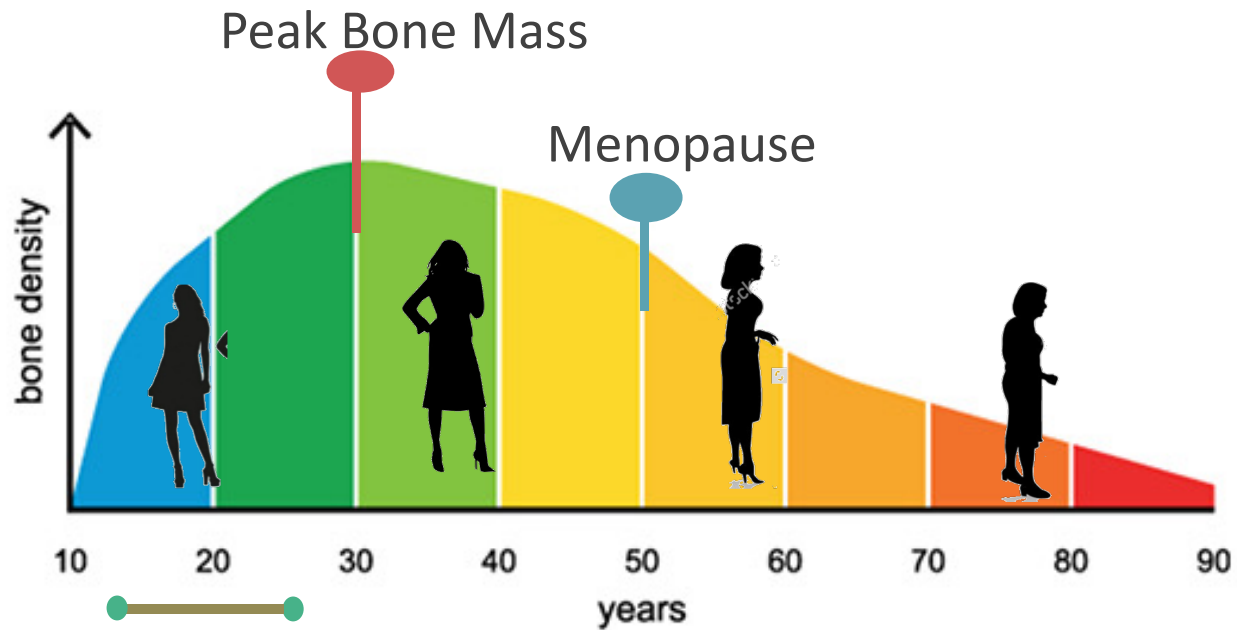




Turnover of the bone



How the Skeleton Changes



Rapid Bone
Building



Risk Factors for Osteoporosis

Things you **can't** change

- 1 Gender
- 2 Heredity
- 3 Age
- 4 Fracture history
- 5 Medical conditions
- 6 Medications



Risk Factors for Osteoporosis

Things you **can** change

- 1 Calcium consumption
- 2 Vitamin D intake
- 3 Quit smoking or vaping
- 4 Alcohol consumption
- 5 Physical activity
- 6 Posture
- 7 Low body weight (BMI <20)
- 8 Some medications



Conditions That Cause Bone Loss

- Alcoholism
- Cancers
- Celiac Disease
- Crohn's Disease
- Cushing's Disease
- Diabetes Type II
- Disordered eating
- Hyperthyroidism
- Hypogonadism
- Liver Disease
- Malabsorption
- Rheumatoid Arthritis



Medications That Cause Bone Loss

- Anticoagulants (Heparin)
- Anticonvulsants (Dilantin)
- Aromatase inhibitors
- Androgen deprivation therapy
- Chemotherapy drugs
- Cyclosporine
- Lithium
- Methotrexate
- PPIs (Nexium, Prilosec, Zantac)
- SSRIs (Prozac, Zoloft, Paxil)
- Oral steroids (Prednizone)
- Tamoxifen (premenopausal use)
- Thyroxine - high doses (Synthroid)

Diagnosing Osteoporosis

- Laboratory Data
 - Limited value in diagnosis
 - Markers of bone turnover (telopeptide) more useful in monitoring effects of treatment than in diagnosis
 - Helpful to exclude secondary causes
 - Hyperthyroidism
 - Hyperparathyroidism
 - Estrogen or testosterone deficiency
 - Malignancy
 - Multiple myeloma
 - Calcium/Vitamin D deficiency

How You Might Know Your Risk

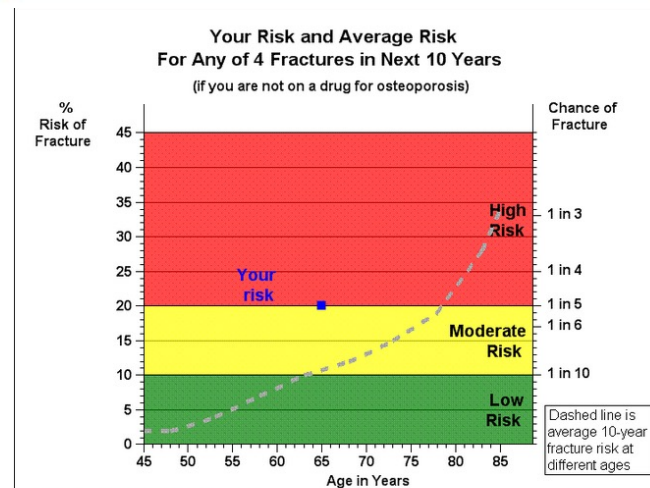
- Low Impact Fracture
- More than 1½" Height Loss
- FORE Fracture Risk Calculator™

The calculator gives an estimate of your risk of breaking a bone.



10-Year Fracture Risk Calculator

www.americanbonehealth.org



Your 10-year risk of any fracture is 20%.
Your 10-year risk of hip fracture is 3%.

[Printable Version](#)
[Questions for your Doctor \(PDF\)](#)

How You Know For Sure

Get a Bone Mineral Density Test

(also known as DXA)

Covered benefit for

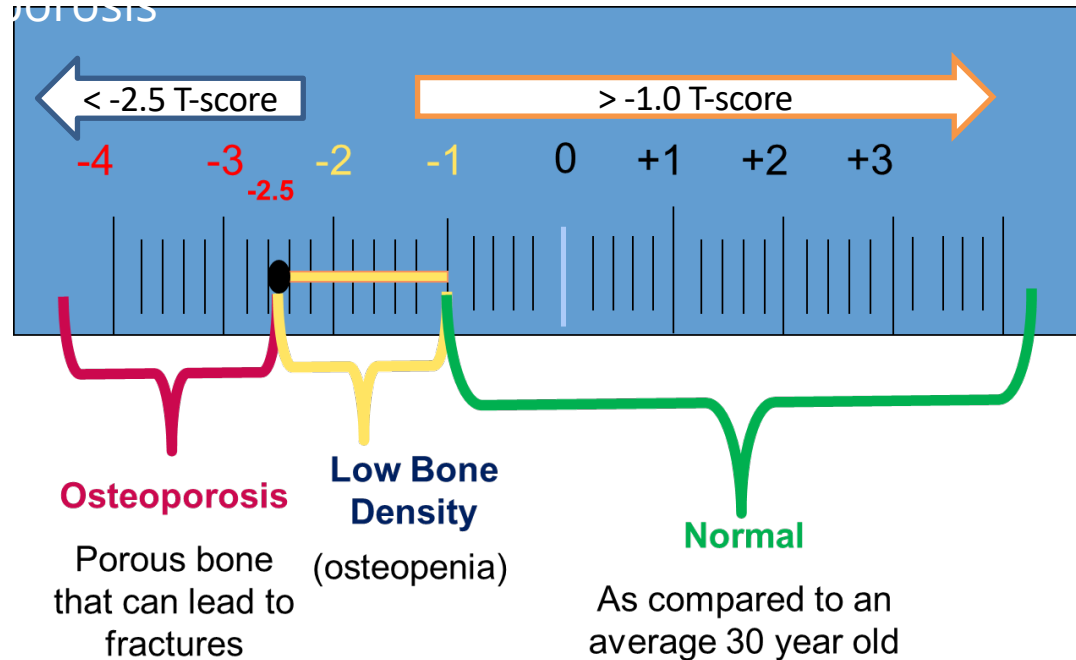
- ✓ Women age 65+
- ✓ Men age 70+
- ✓ Anyone younger with a risk factor



This simple and painless test takes about 15 minutes.



Understanding Your DXA Results



*Even though you may have a low bone density,
you may not have an increased fracture risk.
Your peak bone density may never have reached the "normal" range.*

DXA Lumbar Spine

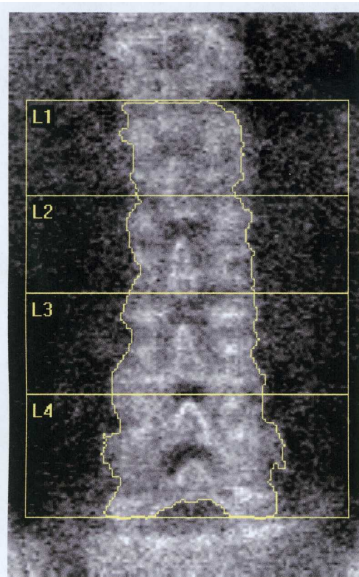


Image not for diagnostic use
k = 1.139, d0 = 43.5
116 x 150

DXA Results Summary:

Region	Area (cm ²)	BMC (g)	BMD (g/cm ²)	T - Score	Z - Score
L1	13.17	9.12	0.692	-2.9	-1.0
L2	14.83	11.09	0.748	-3.5	-1.3
L3	17.67	15.83	0.896	-2.7	-0.4
L4	24.95	23.23	0.931	-2.7	-0.3
Total	70.63	59.27	0.839	-2.8	-0.6

Total BMD CV 1.0%, ACF = 1.029, BCF = 0.999, TH = 9.033

WHO Classification: Osteoporosis

Fracture Risk: High

DXA Hip

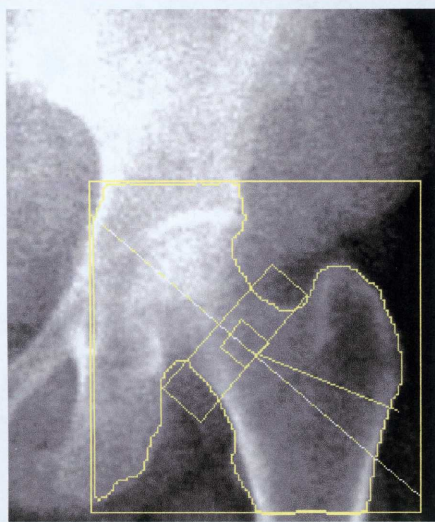


Image not for diagnostic use
k = 1.144, d0 = 46.9
97 x 98

DXA Results Summary:

Region	Area (cm ²)	BMC (g)	BMD (g/cm ²)	T - Score	Z - Score
Neck	4.50	2.69	0.597	-2.5	-1.1
Trochanter	11.04	4.96	0.449	-2.5	-1.5
Inter	16.15	12.17	0.754	-2.5	-1.4
Total	31.69	19.82	0.625	-2.6	-1.5
Ward's	1.17	0.54	0.463	-2.5	-0.4

Total BMD CV 1.0%, ACF = 1.029, BCF = 0.999, TH = 7.403

WHO Classification: Osteoporosis

Fracture Risk: High

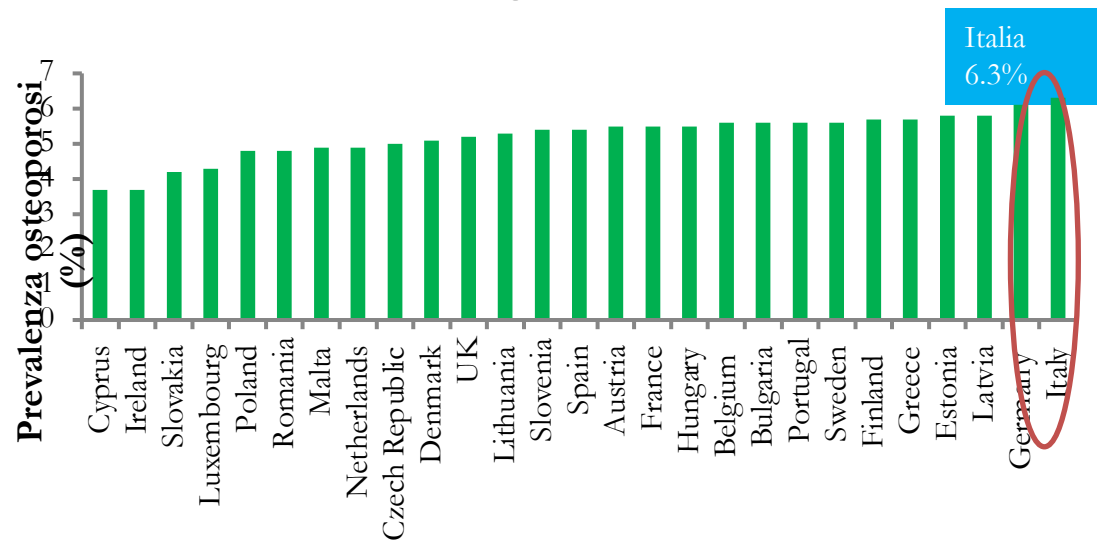
Methods to evaluate for osteoporosis

- **Quantitative Ultrasonography**
- **Quantitative computed tomography**
- **Dual Energy X-ray Absorptiometry (DEXA)**
 - “gold standard”
 - Measurements vary by site
 - Heel and forearm: easy but less reliable (outcome of interest is fracture of vertebra or hip!)
 - Hip site: best correlation with future risk hip fracture
 - Vertebral spine: predict vertebral fractures; risk of falsely HIGH scores if underlying OA/osteophytes

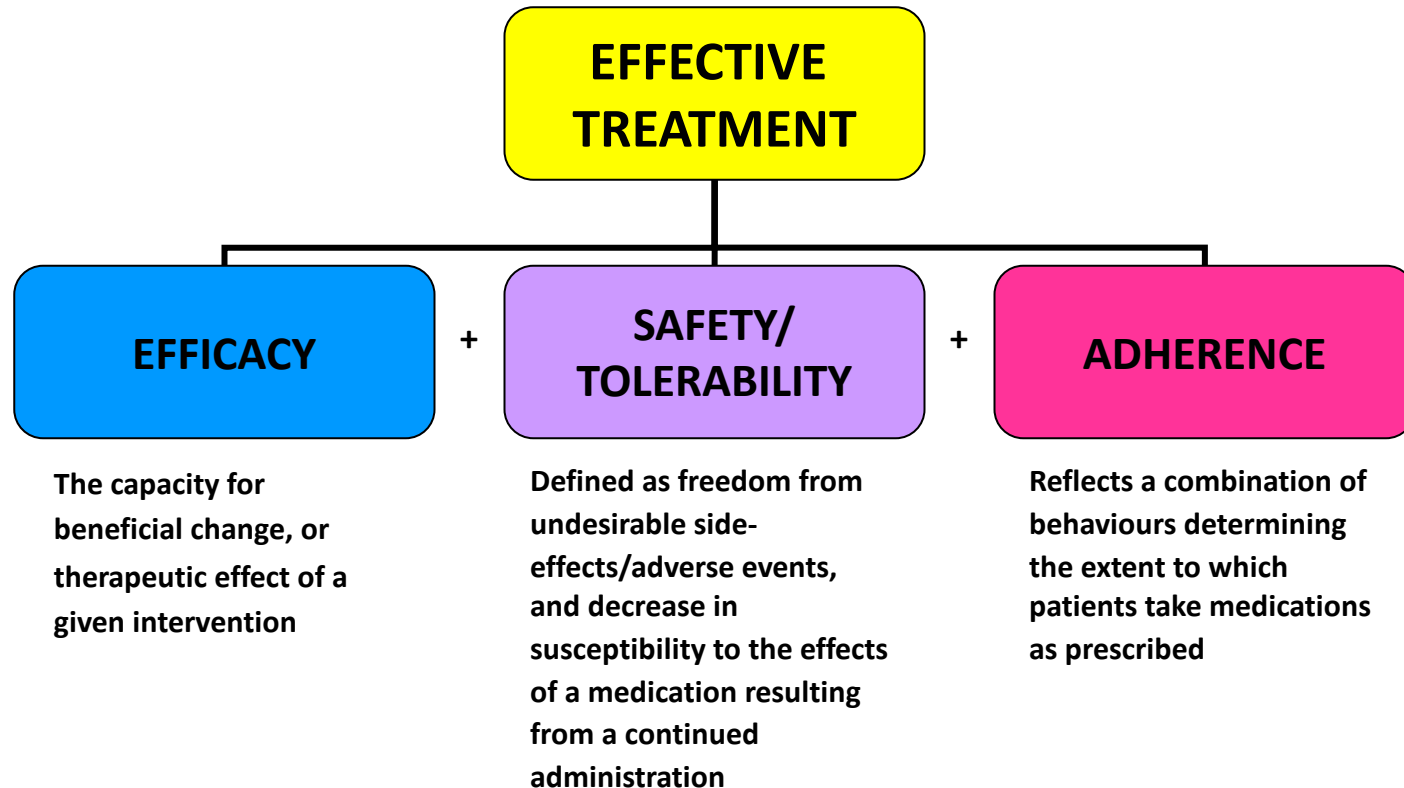
How to interpret the BMD

- **T score: standard deviation of the BMD from the average sex matched 35-year-old**
- **Z score: less used; standard deviation score compared to age matched controls**
- **WHO: Osteoporosis: T score < -2.5**
- **Osteopenia: T score -1 - -2.5**
- **For every 1 decrease in T score, double risk of fracture**
- **1 SD decrease in BMD = 14 year increase in age for predicting hip fracture risk**
- **Regardless of BMD, patients with prior osteoporotic fracture have up to 5 times risk of future fracture!**

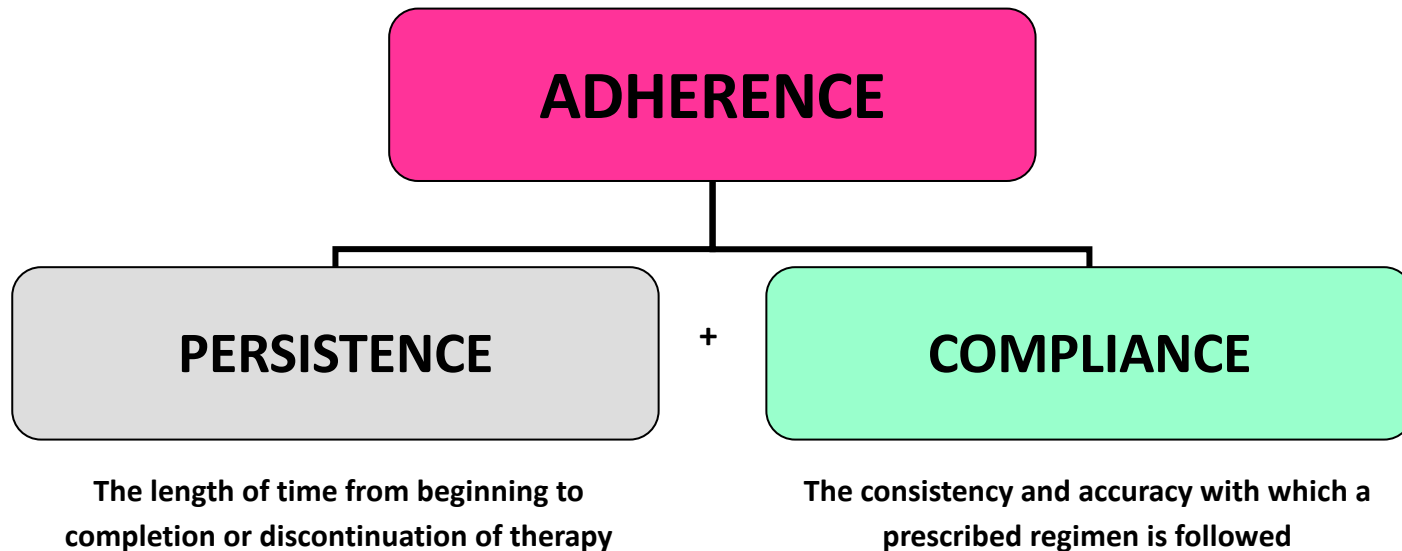
Europe: prevalence of Osteoporosis



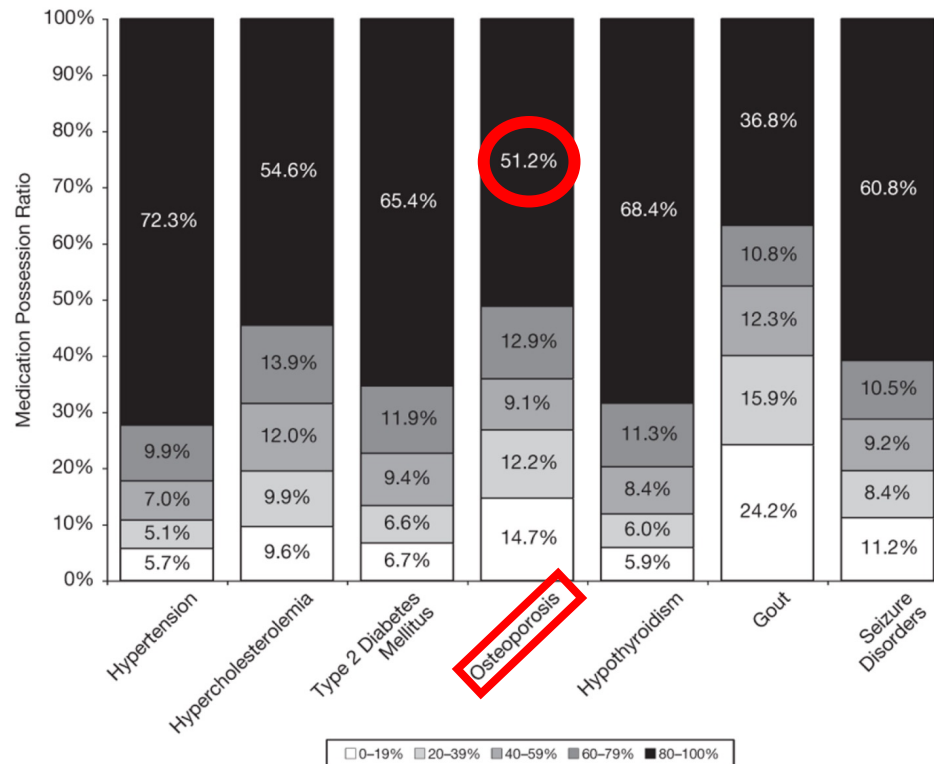
Effective treatment is based on Efficacy, Safety/Tolerability and Adherence



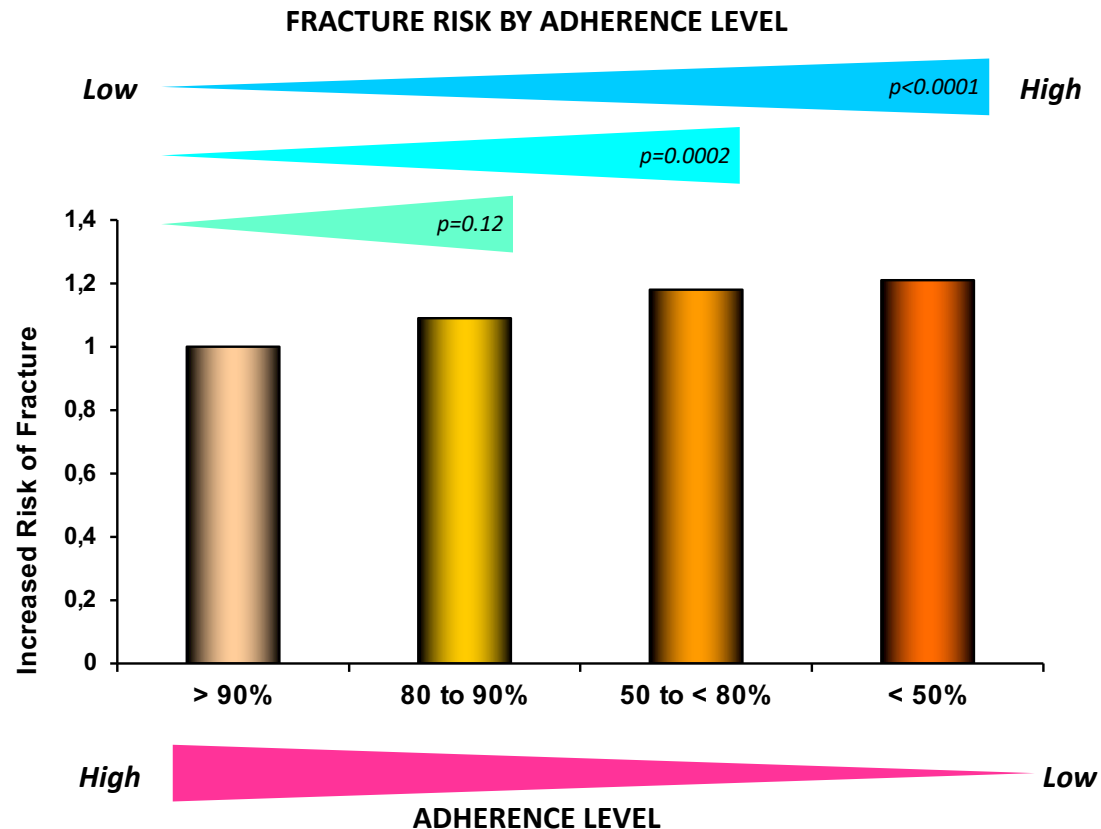
Adherence Encompasses Both Persistence and Compliance



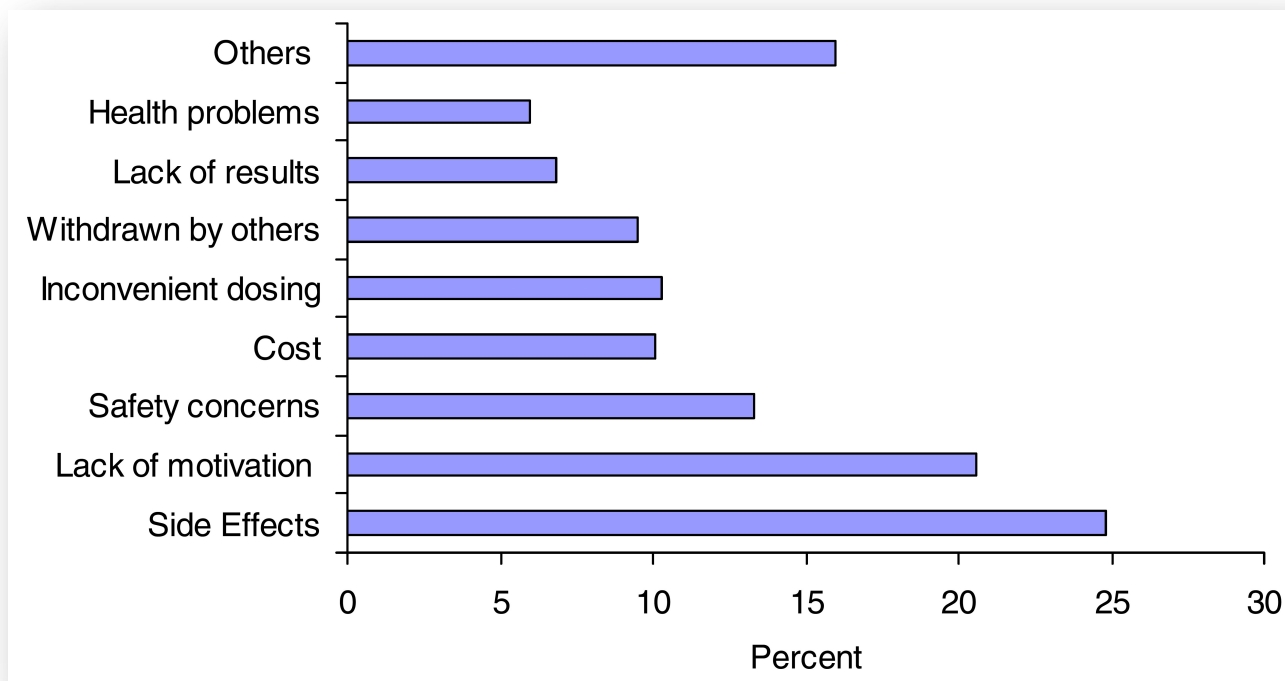
Comparison of drug adherence rates across seven medical conditions



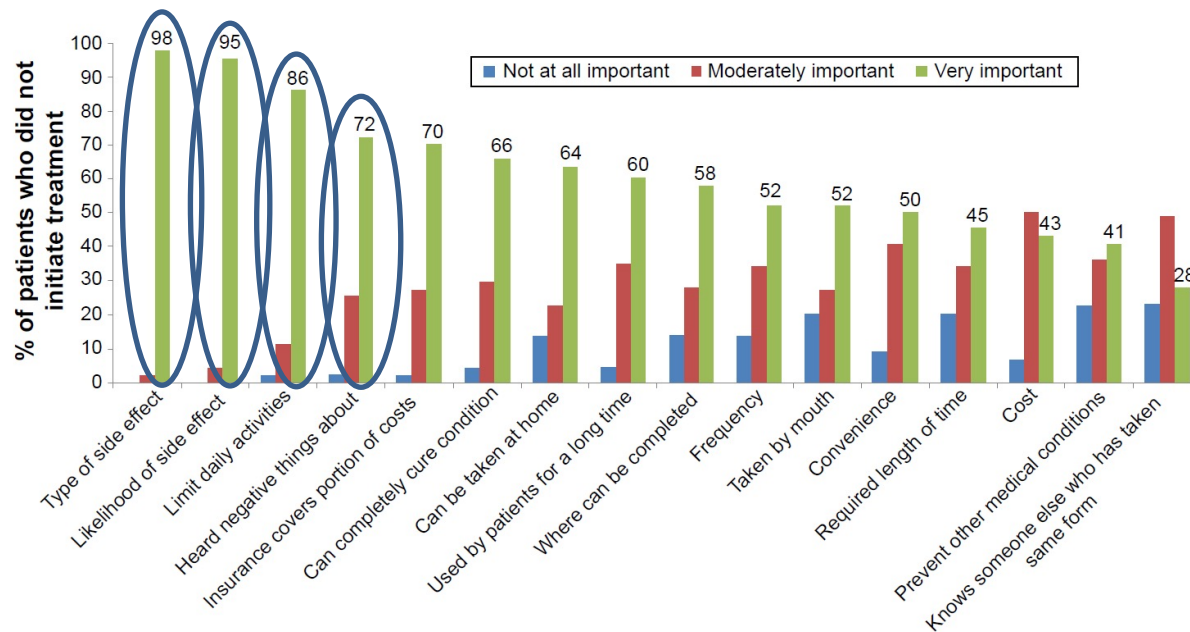
Poor Adherence is Associated with Increased Fracture Risk



Reasons for osteoporosis treatment discontinuations



Reasons for not initiating osteoporosis therapy among a managed care population



Calcium is the Principle Mineral of Bone

- Nerves and muscles need calcium to function;
if not available, the body will take calcium from bones
- The current RDA is 1,000-1,200 milligrams per day
- 3-4 servings of a calcium rich food = 1,000 - 1,200 mg



Dietary Sources of

Food	Item	Calcium Range
Dairy	Low Fat Yogurt, Milk, Cheese	150-400 mg
Proteins	Tofu (with Calcium), Sardines (With Bones), Garbanzo Beans, Almonds	75 - 400 mg
Vegetables	Collards, Bok Choy, Kale, Broccoli	20-260 mg
Other Foods	Pizza, Lasagna, Mineral Water (Gerolsteiner), Dried Figs	120 - 450 mg

How To Read a Nutrition Label

Add a zero to the calcium %
to get milligrams per serving.

$$20\% + 0 = 200 \text{ mg}$$

Nutrition Facts	
Serving Size 2/3 cup (55g)	
Servings Per Container About 8	
Amount Per Serving	
Calories 230	Calories from Fat 72
% Daily Value*	
Total Fat 8g	12%
Saturated Fat 1g	5%
Trans Fat 0g	
Cholesterol 0mg	0%
Sodium 160mg	7%
Total Carbohydrate 37g	12%
Dietary Fiber 4g	16%
Sugars 1g	
Protein 3g	
Vitamin A	10%
Vitamin C	8%
Calcium	20%
Iron	45%
* Percent Daily Values are based on a 2,000 calorie diet. Your daily value may be higher or lower depending on your calorie needs.	
	Calories: 2,000 2,500
Total Fat	Less than 65g 80g
Sat Fat	Less than 20g 25g
Cholesterol	Less than 300mg 300mg
Sodium	Less than 2,400mg 2,400mg
Total Carbohydrate	300g 375g
Dietary Fiber	25g 30g

If You Need a Supplement

If you don't eat 2-3 servings of a calcium-rich food every day, you may need a supplement.

- Two types of calcium supplement

Calcium citrate

i.e., Citracal

Easier on stomach,
Take with or without food

Calcium carbonate

i.e., Caltrate

Less expensive,
Take with food

- Body can only absorb 500-600 mg at a time
- Do not take more than 1,500 mg/day




Vitamin D is Essential

- Calcium needs vitamin D to get absorbed in the intestine
- Sunshine alone is not a reliable source of vitamin D
- RDA varies from 600- 2,000 International Units per day

Food	Item	Vitamin D Range
Fatty Fish	Salmon, Sardines,	150-500 IU
Dairy	Milk, Fortified with D	100-125 IU
Other Foods	Fortified Cereals, Juices	50-75 IU
Protein	Egg Yolk	44 IU

It's very hard to get enough vitamin D through diet!
Supplements are not expensive.



Fracture Reduction

- Goal: prevent fracture, not just treat BMD
- Osteoporosis treatment options:
 - Calcium and vitamin D
 - Bisphosphonates
 - Estrogen replacement
 - Selective Estrogen Receptor Modulators
 - Parathyroid Hormone

Osteoporosis Treatment: Calcium and Vitamin D

- **Fewer than half adults take recommended amounts**
- **Higher risk: malabsorption, renal disease, liver disease**
- **Calcium and vit D supplementation shown to decrease risk of hip fracture in older adults**
- **1000 mg/day standard; 1500 mg/day in postmenopausal women/osteoporosis**
- **Vitamin D (25 and 1,25): 400 IU day at least;**
 - **Frail older patients with limited sun exposure may need up to 800 IU/day**

Osteoporosis Treatment: Bisphosphonates

- Decrease bone resorption
- Multiple studies demonstrate decrease in hip and vertebral fractures
- Alendronate, risodronate
- IV: pamidronate, zoledronate (usually used for hypercalcemia of malignancy, malignancy related fractures, and multiple myeloma related osteopenia)
- Ibandronate (boniva): once/month
- Those at highest risk of fracture (pre-existing vertebral fractures) had greatest benefit with treatment

Bisphosphonate Associated Osteonecrosis (BON)

- Jaw osteonecrosis
- Underlying significant dental disease
- Usually associated with IV formulations
- Case reports associated with oral formulations

Bisphosphonates: Contraindications

- Renal failure
- Esophageal erosions
 - GERD, benign strictures, most benign GI problems are NOT a contraindication
 - Concern for esophageal irritation/erosions from direct irritation, recommendations to drink water after and not lie down at least 30 minutes
 - Reality: no increased GI side effects compared to placebo group in multiple studies

Osteoporosis Treatment: Estrogen Replacement

- Reduction in bone resorption
- Proven benefits in treatment
- FDA approval, now limited because of recent concerns from HERS trial and other data suggesting possible increased total risks with HRT (?increased cardiac risk, increased risk VTE, increased risk cancer)

Osteoporosis Treatment: Selective Estrogen Receptor Modulators

- Raloxifene
- FDA recommended
- Decrease bone resorption like estrogen
- No increased risk cancer (decrease risk breast cancer)
- Increase in vasomotor symptoms associated with menopause

Osteoporosis Treatment: PTH

- Teriparatide
- INTERMITTENT PTH: overall improvement in bone density
 - Optimal bone strength relies upon balance between bone breakdown and bone build up; studies with increased density but increased fracture risk/fragility with fluoride show that just building up bone is not enough!!!

Intermittent PTH: Teriparatide

- Studies suggest improved BMD and decreased fractures
- risk osteosarcoma with prolonged use (over 2 years): studies with rats
- SQ, expensive
- Option for severe osteoporosis, those on bisphosphonates for 7-10 years, those who can not tolerate oral bisphosphonate
- Optimal effect requires bone uptake
- Not for use in combination with Bisphosphonate!
 - May need to stop bisphosphonate up to 1 year prior

Current Guidelines

- **US Preventive Task Force**
 - Test Bone Mineral Density in all women over age 65, younger postmenopausal women with at least one risk factor, and postmenopausal women with a history of fracture
 - Treat patients with T score <-2 and no risk factors, T score <1.5 if any risk factors, and anyone with prior vertebral/hip fracture

Who is left out?

- **Older men**
 - Not included in recommendations
 - Screening not recommended or paid for
 - Significant problem, risk of osteoporosis, risk of fracture, especially after age 70, even more so after age 80
 - Significant evidence that men with osteoporosis benefit from treatment