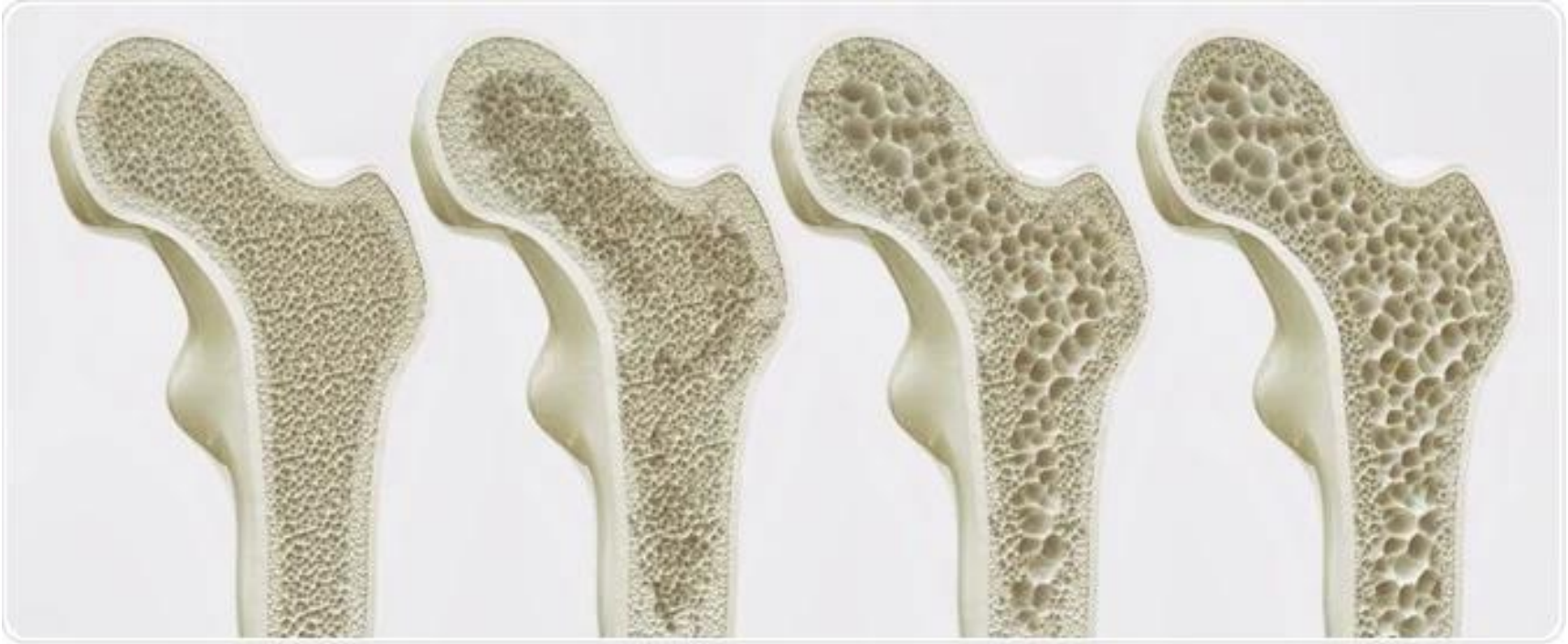

Osteoporosis

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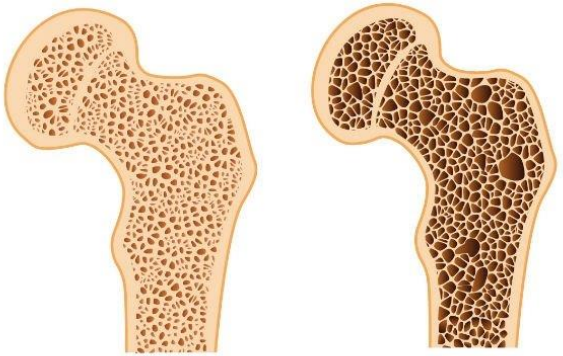
Incidence, Prevalence, and Epidemiology

Osteoporosis is a well-recognized disorder of reduced bone strength leading to an increased risk of **fractures**. It is the *most common bone disease* in humans, characterized by low bone mass and a deterioration of bone tissue.

Osteoporosis is considered a **silent disease** and can progress *without symptoms* until a fracture occurs. Fractures of the *spine*, *hip*, and *wrist* are the most common and may be followed by a complete recovery, considerable pain and disability, or death.



Incidence, Prevalence, and Epidemiology

Conditions that contribute to primary osteoporosis are prolonged periods of inadequate calcium intake, sedentary lifestyle, and tobacco and alcohol abuse.

Secondary osteoporosis is the deterioration of bone mass that is associated with **chronic conditions** or from the use of various medications.

Types of osteoporosis

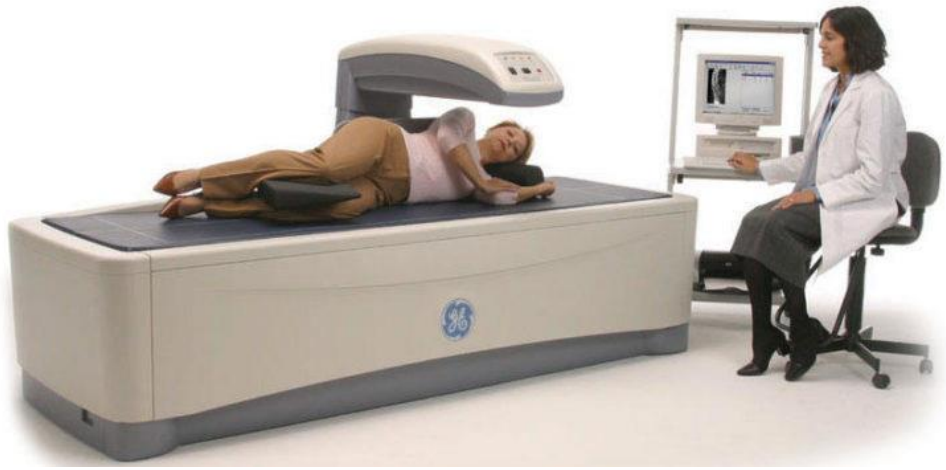
Primary osteoporosis
- idiopathic juvenile osteoporosis
- postmenopausal osteoporosis
- senile osteoporosis

Secondary osteoporosis
- Endocrine origin
  - hypogonadism
  - hypercortisolism (steroid medication, Cushing syndrome)
  - hyperthyroidism
  - hyperparathyroidism
  - hyperprolactinemia
  - diabetes mellitus
- Gastrointestinal diseases
  - chronic inflammatory bowel diseases
  - malabsorption
  - malnutrition
  - primary biliary cirrhosis
  - lactose intolerance
- Bone marrow diseases
  - multiple myeloma (plasmacytoma)
  - diffuse bone metastases
- Rheumatological and connective tissue diseases
  - rheumatoid arthritis
  - osteogenesis imperfecta
  - Ehlers–Danlos syndrome
  - Marfan syndrome
  - homocystinuria
- Other causes
  - immobilization
  - chronic alcoholism
  - organ transplantation
  - other

Incidence, Prevalence, and Epidemiology

The standard method of identifying osteoporosis is the measurement of **bone mineral density (BMD)** at either the femur neck region of the proximal femur (hip) or the lumbar spine.

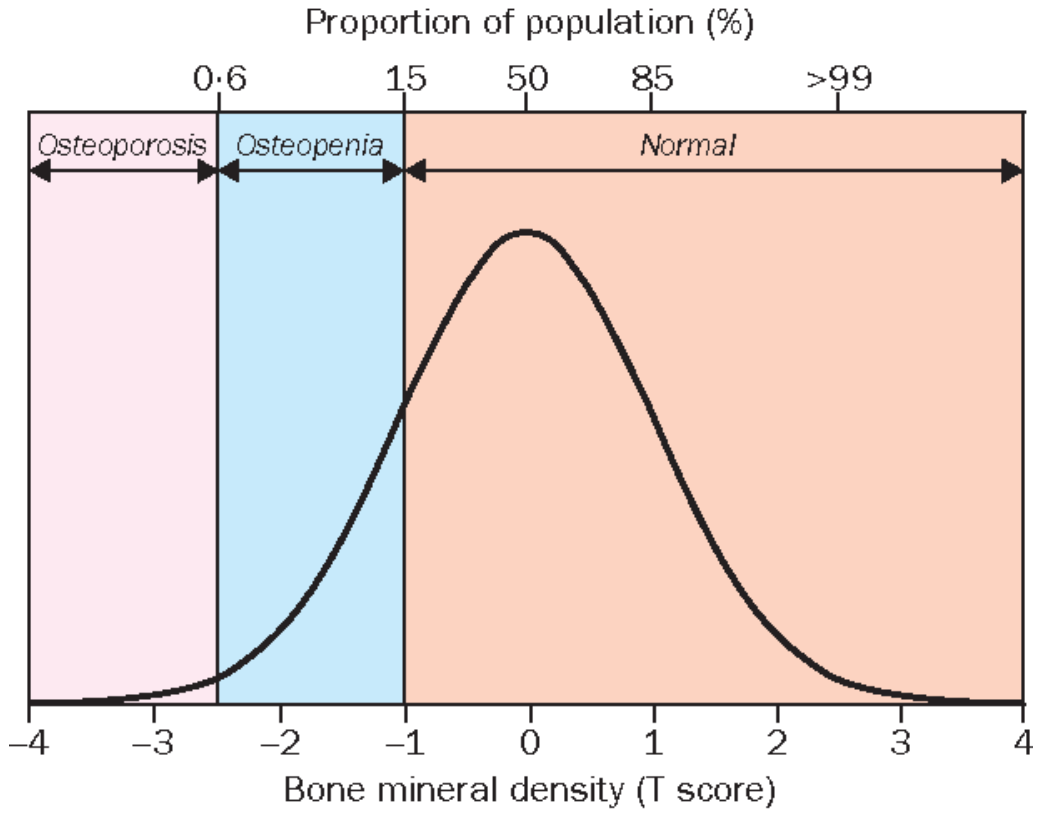
BMD is reported as T-score and also as Z-score. As T-score is a comparison of BMD to what is expected in a young healthy adult population of the same gender, Z-score is a comparison of BMD to what is expected in a healthy adult population of a similar age, gender, and ethnicity.



Incidence, Prevalence, and Epidemiology

When measured by dual-energy X-ray absorptiometry (DXA), a bone mineral density that lies **2.5 standard deviations or more** *below the average* value for young healthy women, a T-score of **less than −2.5 SD**, is considered **osteoporosis** and an effective method to identify patients at increased risk for fracture.

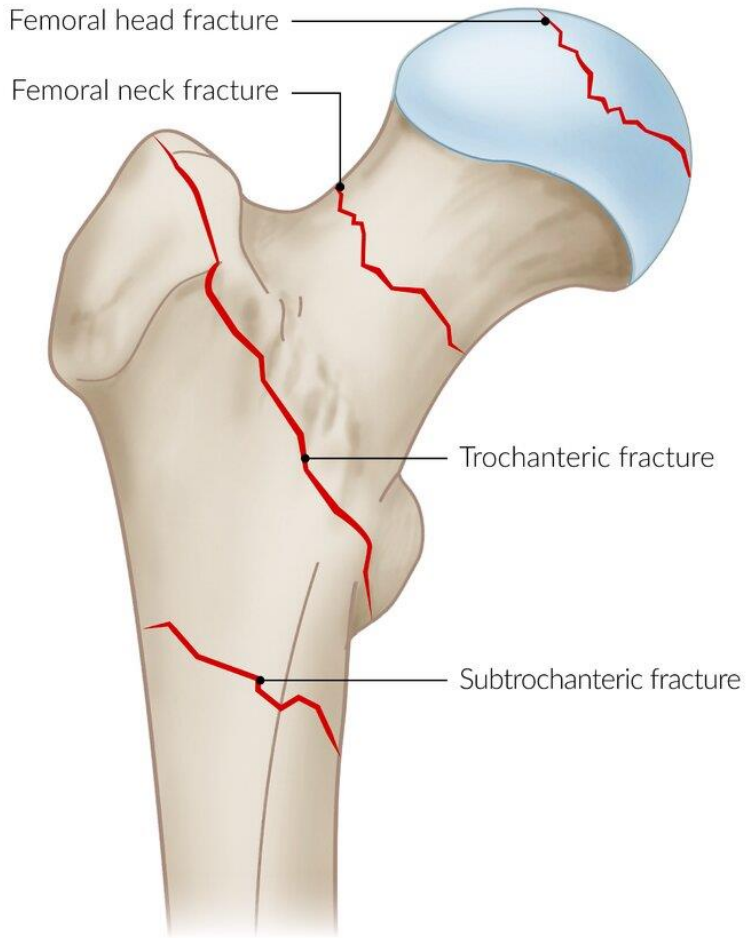
As the T-score decreases, the risk for fracture increases. A T-score *between −2.5 and −1* is defined as **osteopenia**, but is better referred to as low bone mass or low bone density. A T-score greater than or equal to −1 is considered normal.



Incidence, Prevalence, and Epidemiology

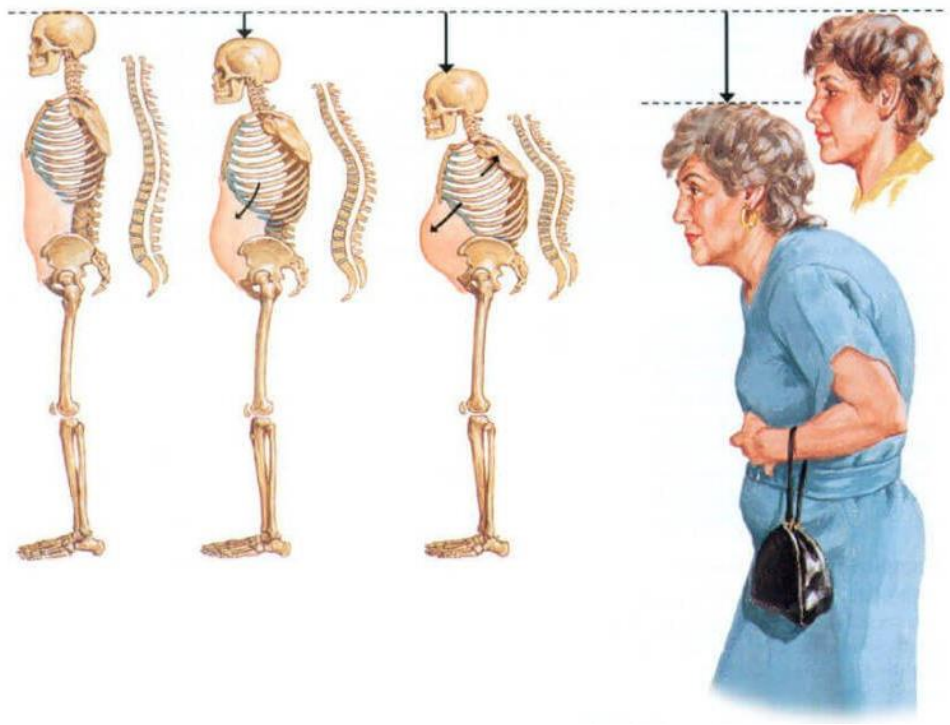
Hip fractures have a profound impact on the quality of life and a considerable associated *mortality*.

The mortality during the first year after hip fracture is as high as **36%** with a higher mortality in men than women.



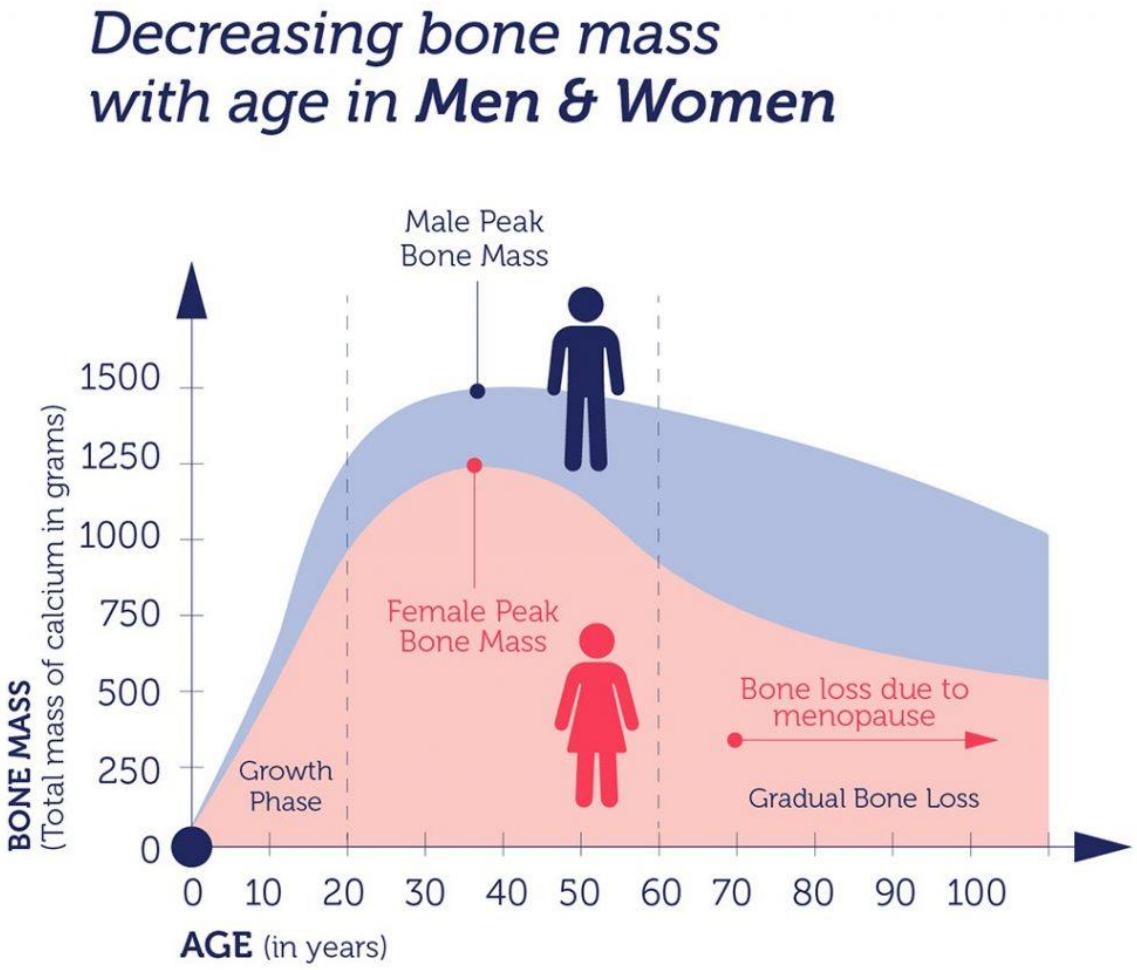
Incidence, Prevalence, and Epidemiology

Vertebral fractures may be *painless* or result in *pain* that usually lasts less than 3 months. The initiating injury may be as minor as a **cough** or **turning over in bed**. The risk of additional vertebral fractures is high.



Vertebral collapse or deformity can result in *loss of height*, kyphosis, abdominal protuberance, or decreased pulmonary function as the abdominal cavity is shortened, chronic back pain, decreased mobility, or mortality.

Etiology


Decreasing bone mass
with age in Men & Women
Male Peak
Bone Mass
Female Peak
Bone Mass
Bone loss due to
menopause
Growth
Phase
Gradual Bone Loss
BONE MASS
(Total mass of calcium in grams)
1500
1250
1000
750
500
250
0
0 10 20 30 40 50 60 70 80 90 100
AGE (in years)

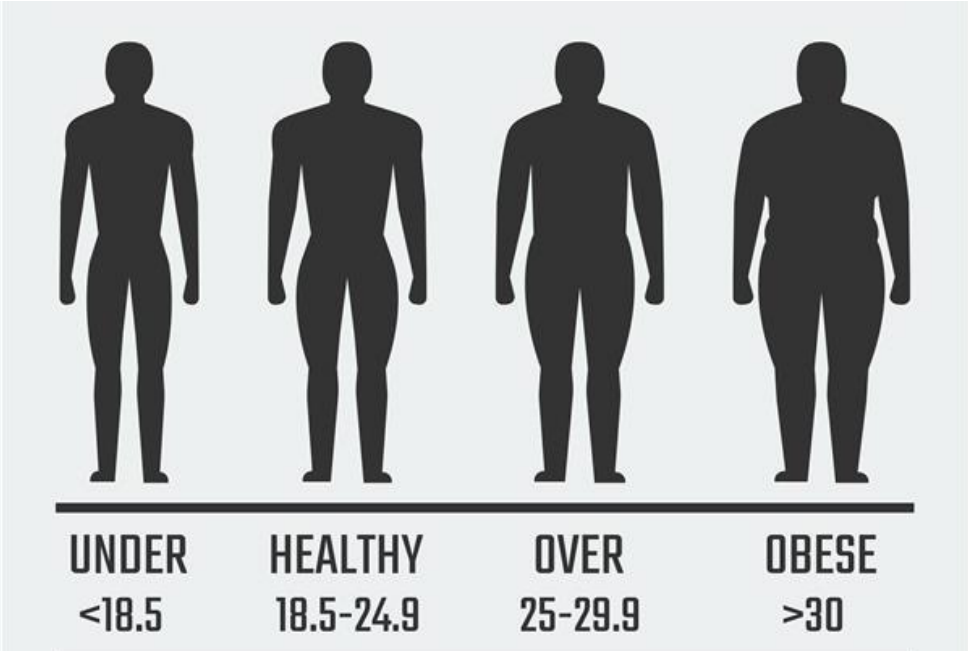
Pathophysiology

Calcium and vitamin D are important nutrients required for bone growth. Parathyroid hormone (PTH), glucocorticoid hormones, calcitonin, estrogen, and testosterone are all factors involved in bone remodeling. **Parathyroid hormone** and **glucocorticoid** hormones have been associated with *bone resorption*, whereas **calcitonin**, **estrogen**, and **testosterone** have been associated with *bone formation*.

Risk Factors

Low Body Mass

Low body mass index (BMI less than 20) is an established independent risk factor for osteoporosis and fracture. Nevertheless, *obesity* should **not** be considered a protective factor.



Risk Factors

Family History and Genetic Factors

A family history of osteoporotic fracture is believed to be an underlying genetic predisposition. *Small stature* or height is inherited.

Certain **disease states** are genetic and have an associated risk of osteoporosis (e.g., celiac disease—a disorder associated with malabsorption). **Genetic factors** associated with osteoporosis may be related to peak bone mass, polymorphisms in the vitamin D receptor, genes associated with estrogen deficiency or estrogen resistance, bone morphogenetic proteins, signaling pathways, and various other bone-related proteins and receptors.

Risk Factors

Mobility and Physical Activity

Bone mass is dependent on physical activity. Prolonged **immobility** of a limb or prolonged bed rest can result in a *loss of skeletal tissue* and bone mass.

The NOF recommends a combination of regular *weight-bearing exercise* and *muscle-strengthening exercise* to increase strength and reduce the risk of falls and fractures. These include walking, jogging, Tai Chi, stair climbing, dancing, tennis, weight training, and other resistive exercises.

Risk Factors

Cigarette Smoking and Alcohol Ingestion

Women and men who **smoke** have an increased risk for fractures, including hip fractures, compared with nonsmokers. Smoking *impairs the absorption* of dietary and supplemental calcium, lowers body weight, influences estrogen metabolism, and may be directly toxic to bone cells.

Excessive *alcohol* use by both women and men is associated with decreased BMD. The effect of alcohol on bone is *dose dependent*; consuming more than two alcoholic drinks daily significantly increases the fracture risk.

Risk Factors

Dietary Intake

Dietary *calcium* and *vitamin D* are critical to bone health and needed to strengthen bones and increase bone mass.

The Institute of Medicine of the National Academies published recommendations for both calcium and vitamin D intake that would promote bone maintenance along with a neutral calcium balance based on age. Calcium is best ingested from the diet.

Dietary Reference Intakes for Calcium and Vitamin D[33]

Life Stage Group	RDA Calcium	RDA Vitamin D
Males		
19–50 years	1,000 mg	600 IU (15 mcg)
51–70 years	1,000 mg	600 IU (15 mcg)
>70 years	1,200 mg	600 IU (15 mcg)
Females (Nonpregnant)		
19–50 years	1,000 mg	600 IU (15 mcg)
51–70 years	1,200 mg	600 IU (15 mcg)[a]
>70 years	1,200 mg	800 IU (20 mcg)[a]

[a]NOF recommends vitamin D 800 to 1,000 IU in patients ≥ 50 years.
IU, International Unit; RDA, Recommended Dietary Allowance.

Risk Factors

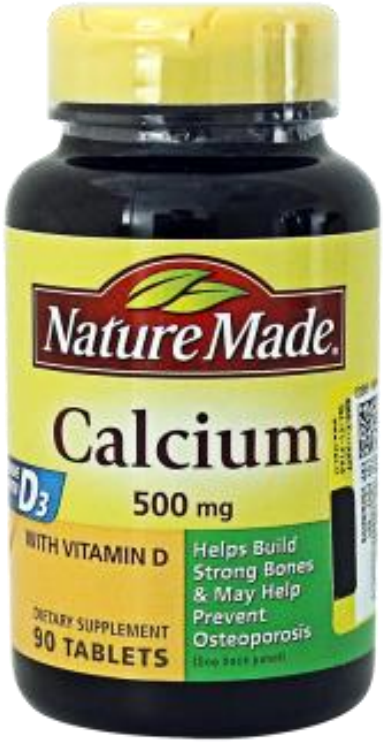
The National Osteoporosis Foundation (NOF) has similar recommendations for calcium and, however, differs in their recommendations for vitamin D intake. Vitamin D **800 to 1,000 international units (IU) per day** is recommended for individuals *50 years of age and older.*

The serum level of 25-OH-D is considered the marker for adequate intake. The National Osteoporosis Foundation recommends vitamin D intake to maintain serum 25-OH-D levels > 30 ng/mL (75 nmol/L). The combination of vitamin D and calcium results in small increases in BMD of the spine, the total body, femoral neck, and total hip.

Risk Factors

There are few adverse effects from vitamin D supplementation. Vitamin D3 combined with calcium can increase the chance of forming **kidney stones** and supplementation with the active form of vitamin D can increase the risks of **hypercalcemia**.

If the calcium or vitamin D in the **diet** does not achieve the recommendations, **supplements** should be added.



Overview of Drug Therapy

Pharmacologic treatment should be considered in patients with low-trauma hip or vertebral fracture, patients with a T-score of ≤ -2.5, and patients with low bone mass who are at increased risk for fracture.

Medications include selective estrogen receptor modulators (SERMs; e.g., raloxifene) and calcitonin in women, bisphosphonates (e.g., alendronate), RANKL inhibitors (e.g., denosumab), and parathyroid hormone for both men and women.

Prevention

PREMENOPAUSAL WOMEN

Universal recommendations for the prevention of osteoporosis are adequate intake of daily *calcium and vitamin D*, weight-bearing and strengthening *exercise*, reduced *alcohol* consumption, and *smoking* cessation.

Prevention

The amount of elemental calcium in supplements varies. Two common forms of calcium supplements are *calcium carbonate* and *calcium citrate*.

The **cost** of calcium carbonate tends to be lower and it contains the highest percentage of elemental calcium (40%).

TABLE 105-3
Percentage of Calcium in Various Salts

Salt	Percent Calcium
Calcium carbonate	40
Tricalcium phosphate (calcium phosphate, tribasic)	39
Calcium chloride	27
Dibasic calcium phosphate dehydrate	23
Calcium citrate	21
Calcium lactate	13
Calcium gluconate	9

Prevention

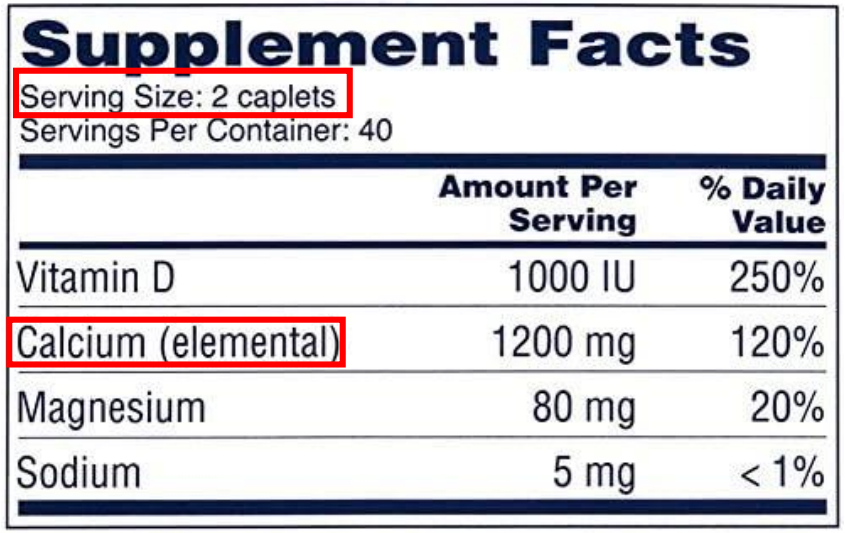
Calcium absorption from supplements depends on the total amount of elemental calcium consumed at **one time**. The percentage of calcium absorbed decreases as the dose increases. *Maximal absorption* occurs at doses ≤ 500 mg at one time.

Calcium carbonate absorption is dependent on *stomach acid* and should be taken *with food*. **Calcium citrate** contains less elemental calcium, 21%, is *less dependent on stomach acid* for absorption, and can be taken *with or without food*. Calcium citrate is beneficial in patients with achlorhydria, inflammatory bowel disease, or in patients taking proton pump inhibitors or histamine 2 receptor blockers.

Prevention

Supplements should be taken with *plenty of fluids*. Calcium can compete or interfere with the absorption of iron, zinc, and magnesium. Significant **drug interactions** can also occur, such as impaired absorption of medications including tetracyclines, thyroid products, and quinolones.

The most common *adverse effects* of calcium are **constipation**, GI irritation, bloating, and flatulence. **Caution** should be used in patients with renal insufficiency, hypoparathyroid disease, hypercalcemia, and a history of kidney stones.



Supplement Facts

Serving Size: 2 caplets

Servings Per Container: 40

	Amount Per Serving	% Daily Value
Vitamin D	1000 IU	250%
Calcium (elemental)	1200 mg	120%
Magnesium	80 mg	20%
Sodium	5 mg	< 1%

INGREDIENTS: Calcium Carbonate, Calcium Citrate, Magnesium Hydroxide, Acacia, Hydroxypropyl Methylcellulose, Croscarmellose Sodium, Magnesium Silicate, Titanium Dioxide (color), Propylene Glycol Dicaprylate/Dicaprate, Magnesium Stearate, Inulin (Oligofructose Enriched), Vitamin D_3 (Cholecalciferol).

Prevention

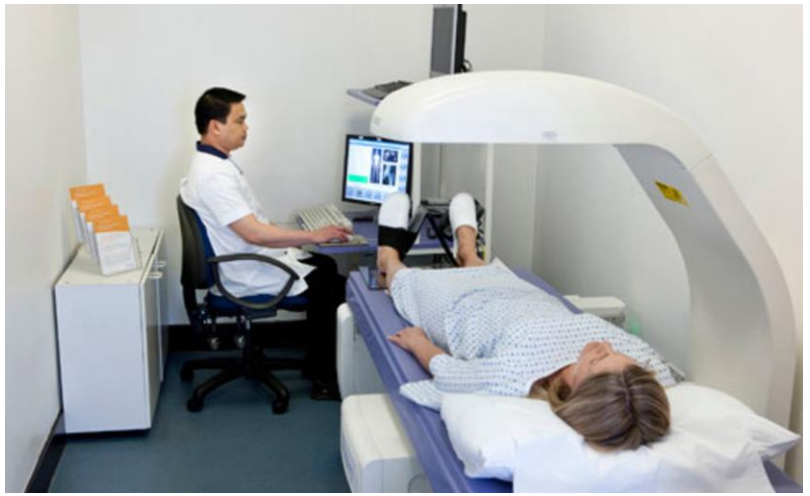
POSTMENOPAUSAL WOMEN

The North American Menopause Society (NAMS) recommends a **BMD measurement** in *women* who are *older than 50 years* of age if *one or more risk factors* for fracture are present.

These risk factors include weight <127 pounds or BMI <21 kg/m^2, fracture other than skull, facial bone, ankle, finger or toe after menopause, first-degree relative with a history of hip fracture, smoking, rheumatoid arthritis, or alcohol consumption of two drinks per day (1 drink = 12 oz of beer, 4 oz of wine, or 1 oz of liquor).

Prevention

NAMS also recommends BMD testing in **postmenopausal** women with bone loss due to *medical conditions* such as hyperparathyroidism, medications such as steroids, postmenopausal women who have had a fragility fracture, and all women over the age of 65.



Prevention

For postmenopausal women who are not receiving medications for osteoporosis prevention, a DXA may be useful no more frequently than **every 2 to 5 years** because the rate of bone loss is approximately 1% to 1.5% per year.

Prevention

The World Health Organization along with several leading osteoporosis organizations developed the WHO Fracture Risk Assessment tool (FRAX) that can be used alone or with BMD to identify fracture risk. FRAX is a computerized-based algorithm created for different populations available online at http://www.shef.ac.uk/FRAX.

The **FRAX algorithm** incorporates *ethnicity* as well as *clinical risk factors* (e.g., age, smoking, physical inactivity, height, weight, prior fracture, parental history of hip fracture, long-term use of glucocorticoids, and comorbid conditions that have been associated with decreases in BMD) to calculate **10-year fracture risk**.

https://www.sheffield.ac.uk/FRAX/tool.aspx?country=68 90%

FRAX® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | CE Mark | English

Calculation Tool

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

Country: Iran Name/ID: 111111111111 About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 50 Date of Birth: Y: 1971 M: 05 D: 14
2. Sex: Male / Female
3. Weight (kg): 76
4. Height (cm): 182
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/cm^2)
    T-Score -1

Clear | Calculate

BMI: 22.9
The ten year probability of fracture (%)
with BMD

Major osteoporotic	4.1
Hip Fracture	0.5

If you have a TBS value, click here: Adjust with TBS

Weight Conversion

Pounds → kg Convert

Height Conversion

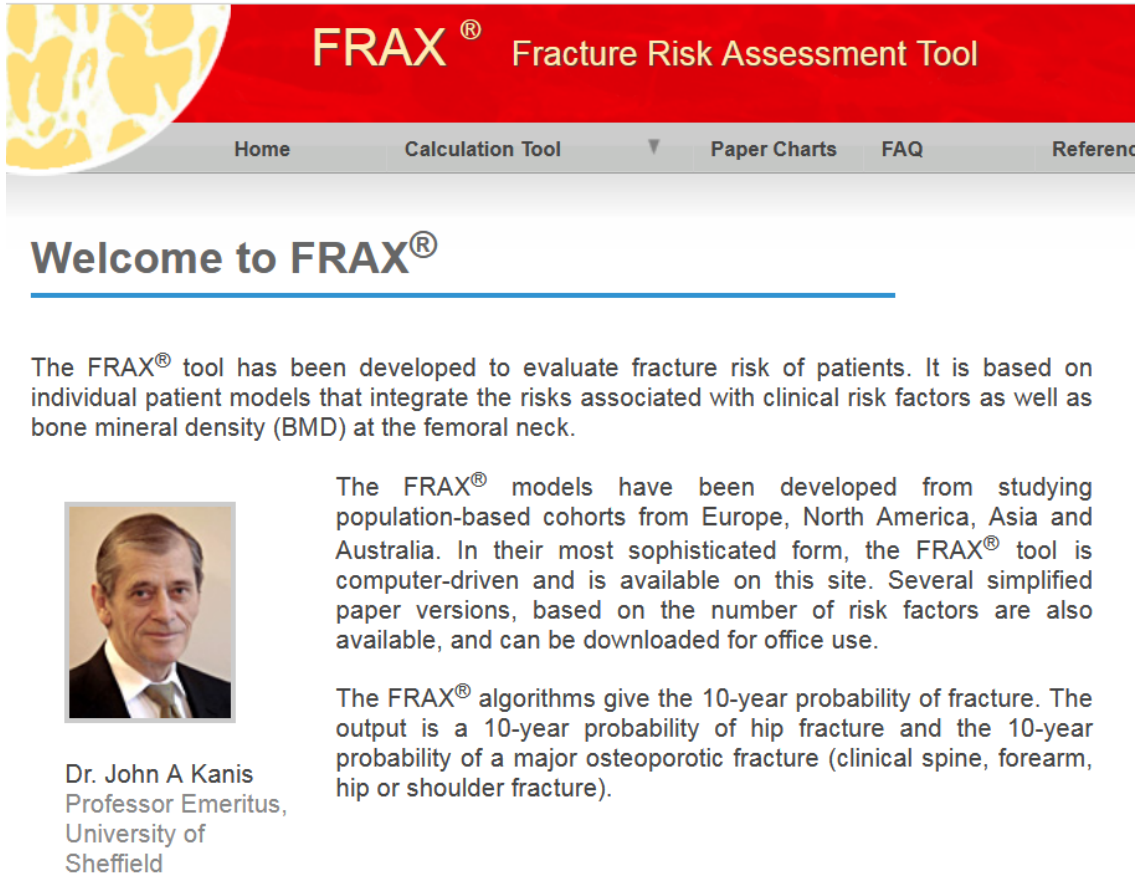
Inches → cm Convert

00178291
Individuals with fracture risk assessed since 1st June 2011

Prevention

FRAX should not replace clinical judgment for treatment and is intended to be used in *postmenopausal women* and *men over age 50*.

It has **not** been validated in patients who have been on or who are receiving **medication** therapy for osteoporosis.



Prevention

Postmenopausal women who incorporated aerobic and weight-bearing **exercise** showed some improvements in BMD and reduced the risk of fractures as compared to those who did not exercise.

The recommended daily allowance of **calcium** for women ages 51 to 70 is 1,200 mg per day. The recommended daily allowance of **vitamin D** for women between 51 and 70 age is 600 IU/day, and for women over age 70, the recommended daily allowance is 800 IU/day. The NOF recommends 800 to 1,000 IU/day for men and women over age 50.

Prevention

Pharmacologic Prevention

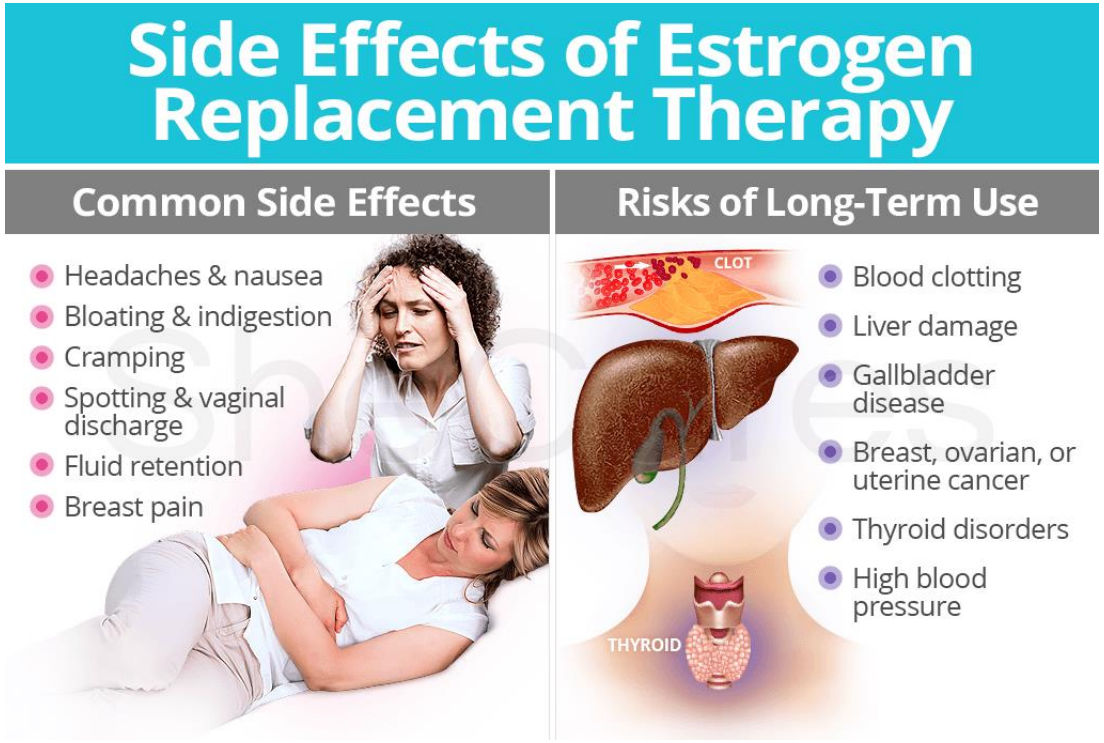
ESTROGEN/PROGESTIN THERAPY

An estimated 10% to 15% of a woman's bone mass is estrogen dependent. Estrogens are important in bone formation, resorption, and maintaining bone mass while menopause is associated with a decrease in estrogen and an increase in bone loss.

Prevention

Previously, ET or EPT would have been considered first-line treatment for the prevention of osteoporosis in postmenopausal women.

Because of the **high rate** of coronary heart disease (CHD), stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and breast cancer, healthcare providers are *less likely* to prescribe ET or EPT for the sole purpose of osteoporosis prevention or to continue its use after a women no longer needs EPT or ET for postmenopausal symptoms such as hot flushes.



Prevention

BISPHOSPHONATES

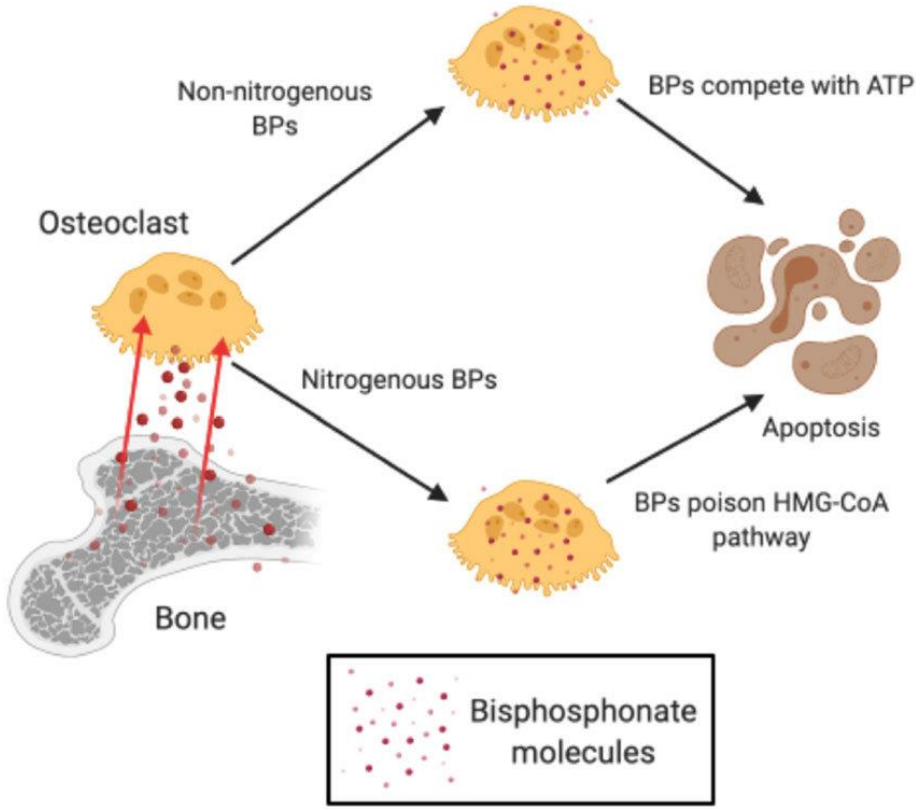
NAMS recommends adding osteoporosis drug therapy in postmenopausal women who have had a vertebral or hip fracture, in postmenopausal women with a BMD of −2.5 or worse at the lumbar spine, femoral neck, or total hip, and in postmenopausal women with a T-score of −1.0 to −2.5 who have a *10-year fracture risk* of 20% (spine, hip, shoulder, wrist) or risk of 3% (hip) calculated using **FRAX**.

Bisphosphonates, analogs of pyrophosphate, are considered *first-line therapy* for the prevention and treatment of osteoporosis in postmenopausal women.

Prevention

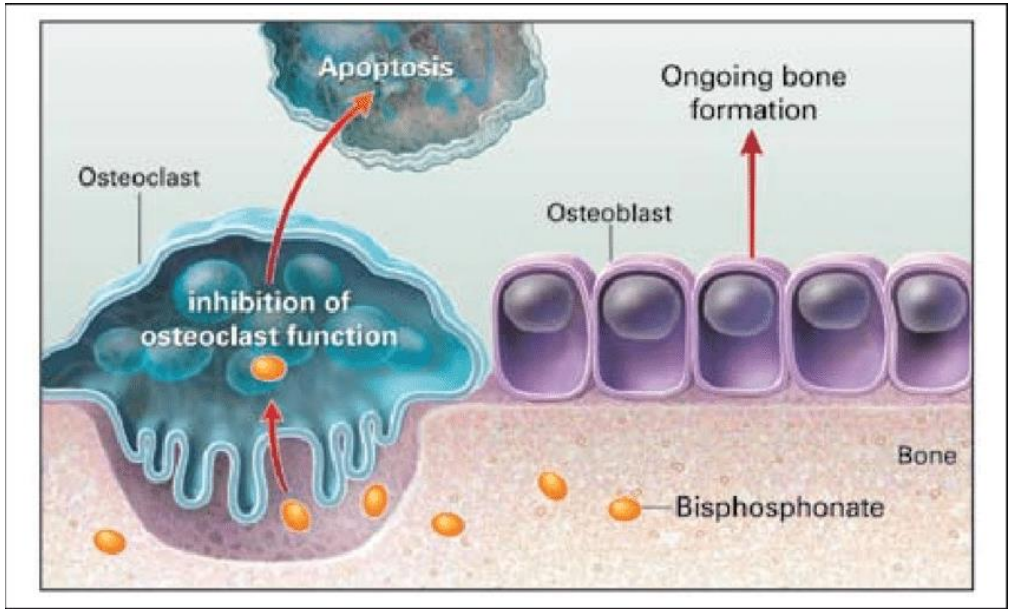
Alendronate, ibandronate, risedronate, pamidronate, and zoledronic acid are aminobisphosphonates with a greater selectivity for the antiresorptive surfaces of the bone due to changes in the nitrogen-containing side chain of the compounds.

Bisphosphonates have high affinities for bone hydroxyapatite and can be incorporated into bone. They **concentrate** in mineral tissue and *interfere* with the osteoclast-mediated bone resorption to cause *osteoclast apoptosis,* decreased bone turnover, resulting in decreased fracture rates in postmenopausal women who are at risk for osteoporosis.



Prevention

Because of their *incorporation into bone*, bisphosphonates have long half-lives, estimated to be **1 to 10 years.** Unlike etidronate (a nonaminobisphosphonate), aminobisphosphonates do not inhibit bone mineralization, which could lead to osteomalacia.



Prevention

Table 5. Overview of FDA-Approved Medications for Osteoporosis

Drug (Brand)	Dosing	Route	Adverse Effects
Bisphosphonates			
Alendronate (Fosamax)	Treatment: 10 mg once daily or 70 mg once weekly Prevention: 5 mg once daily or 35 mg once weekly	Oral	Dyspepsia, abdominal pain, musculoskeletal pain
Ibandronate (Boniva)	Oral: 2.5 mg once daily or 150 mg once a month IV: 3 mg every 3 months	Oral, IV	Dyspepsia, back pain, musculoskeletal pain, headache, abdominal pain
Risedronate (Actonel, Atelvia)	IR: 5 mg once daily or 35 mg once weekly or 150 mg once a month DR: 35 mg once weekly	Oral	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia
Zoledronic acid (Reclast)	5 mg once a year	IV	Acute reaction (flulike symptoms, fever, myalgia) may occur within 3 days of infusion; hypotension, fatigue, eye inflammation, nausea, vomiting, abdominal pain
Calcitonin			
Calcitonin (Fortical)	200 IU in 1 nostril daily alternating each day	Intranasal	Rhinitis, nasal irritation, dizziness, nasal dryness
Calcitonin (Miacalcin)	100 IU every other day 200 IU in 1 nostril daily alternating each day	SC, IM Intranasal	Injection site reactions, nausea, vomiting, abdominal cramping, flushing
Selective Estrogen Receptor Modulator			
Raloxifene (Evista)	60 mg once daily	Oral	VTE, arthralgia, leg cramps, flu syndrome, peripheral edema, hot flashes
Parathyroid Hormone Analogue			
Teriparatide (Forteo)	20 mcg once daily	SC	Transient hypercalcemia, nausea, rhinitis, arthralgia, pain
Monoclonal Antibody			
Denosumab (Prolia)	60 mg every 6 months	SC	Dermatitis, rash, mild bone/muscle pain, UTIs

DR: delayed-release; IM: intramuscular; IR: immediate-release; SC: subcutaneous; UTI: urinary tract infection; VTE: venous thromboembolism.
Source: Reference 7.

Prevention

Zoledronic acid infusion for osteoporosis *prophylaxis* is administered **every other year** as compared to yearly when treating osteoporosis. Oral bisphosphonates are **first-line** and most commonly prescribed medications for the prevention and treatment of osteoporosis.

The incorporation of bisphosphonates into bone results in a *reservoir* of available drug that is slowly released over time. The **peak effect** of reducing bone turnover markers occurs in **3 to 6 months** and continues for months to years with discontinuation.

Prevention

The **ideal duration** of bisphosphonate therapy is *not known*. Bisphosphonates are deposited into the bone and continue to suppress bone turnover after discontinuation, and some adverse effects, such as *atypical fracture*, are associated with duration of therapy.

To balance risk and benefit, some clinicians recommend a "**bisphosphonate holiday**," defined as disruption of therapy during which medication effects exist with a plan for medication reinstitution.

Prevention

Because a beneficial response was predicted by hip T-score, experts recommend that a bisphosphonate holiday could be considered in postmenopausal women after **5 years** of *oral bisphosphonates* or **3 years** of *intravenous bisphosphonates* if no significant fracture history, hip BMD T-score is above –2.5, and fracture risk is not high.

In women with a high-fracture risk or lower hip BMD T-scores, continuing oral bisphosphonates for *10 years* or intravenous bisphosphonates for *6 years* should be considered.

Prevention

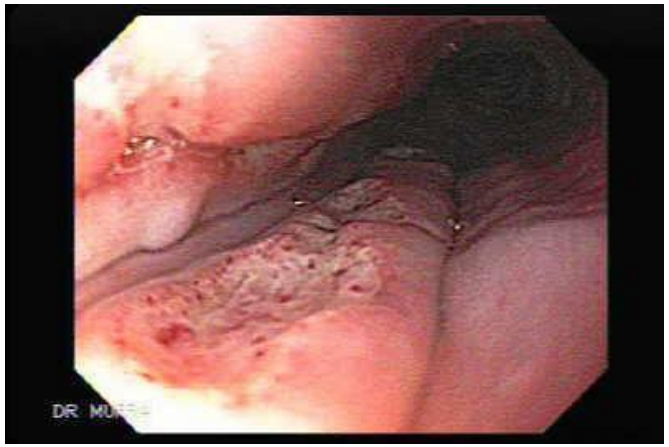
These recommendations are based on limited data and questions remain regarding what therapy to reinitiate and the applicability of this approach for men and patients with glucocorticoid-induced osteoporosis. Bisphosponate holidays should last for 5 or fewer years with *BMD* and *patient assessment* done **every 2 to 4 years**.

Prevention

Common **adverse effects** associated with the use of oral bisphosphonates include gastrointestinal symptoms, such as acid regurgitation, dysphagia, abdominal distension, gastritis, nausea, dyspepsia, flatulence, diarrhea, and constipation. Less common **esophageal adverse effects**, such as esophagitis, esophageal ulcers, and erosions, have occurred and have rarely been followed by esophageal *stricture* or *perforation*. In addition, hypocalcemia, musculoskeletal pain, headaches and rash have been noted.

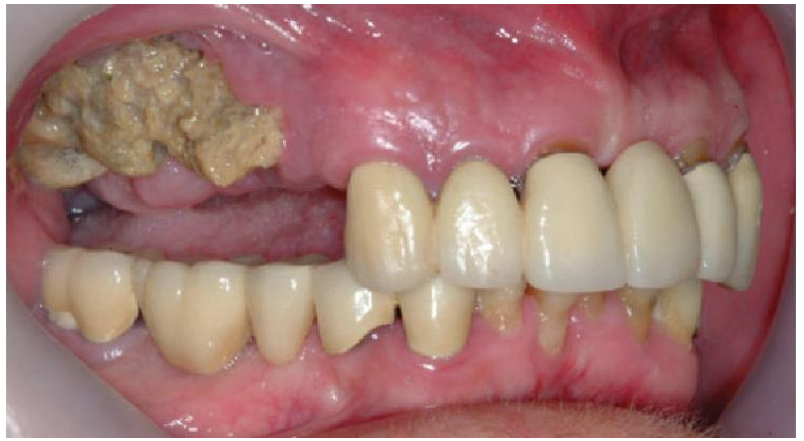
Prevention

The risk of severe esophageal adverse effects is reported to be increased in patients who do not take bisphosphonates with **6 to 8 ounces of water**, do not remain **upright** after taking bisphosphonates, or in those who develop esophageal irritation and continue to take bisphosphonates.



Prevention

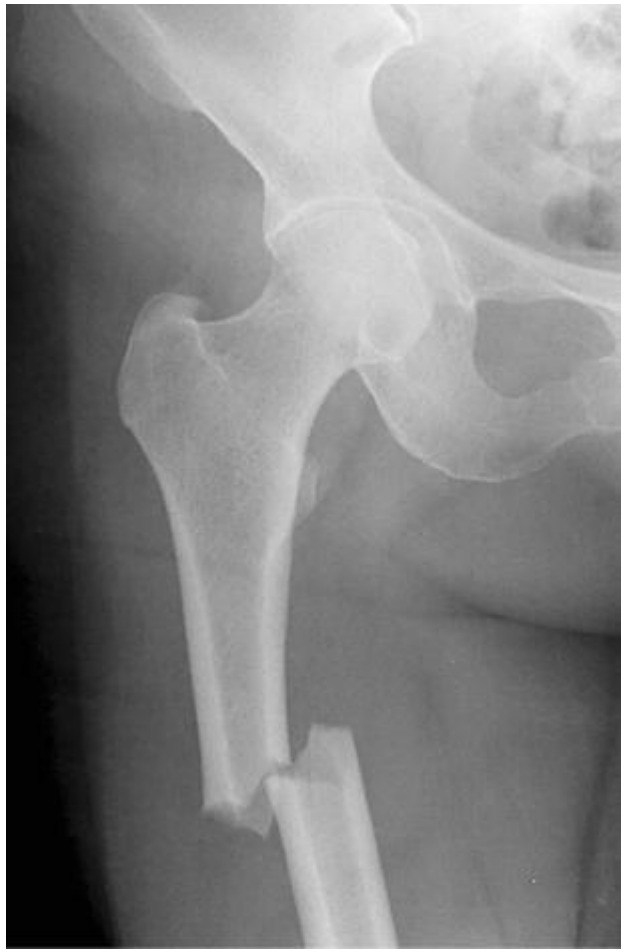
Both *intravenous* (IV) and *oral* bisphosphonates are associated with **osteonecrosis of the jaw** (ONJ), a serious but rare adverse event. Risk factors for osteonecrosis of the jaw include the diagnosis or previous history of cancer; invasive dental procedures; concurrent use of chemotherapy, corticosteroids, or angiogenesis inhibitors; poor oral hygiene; preexisting dental disease or infection; and anemia and coagulopathy. The risk of ONJ increases at higher doses and with duration of exposure.



Prevention

Bisphosphonates are associated with **atypical fractures** of the *femoral shaft*. A **warning** is included in the manufacturers' information for all bisphosphonate drugs that are indicated for the prevention or treatment osteoporosis. A clear connection has not been found.

The mechanism of action is not clear; however, bone is normally subject to *microdamage* with every day stresses and this initiates bone remodeling. Antiresorptive agents may **oversuppress bone turnover** causing microdamage to accumulate which may lead to brittle bone and an increased risk of fracture.



Prevention

Additional adverse effects reported with **zoledronic acid** are pyrexia, headache, pain in extremity, flu-like illness, and eye inflammation.

Prevention

Patients should be instructed to take most bisphosphonates with *6 to 8 ounces of water* early in the morning on arising and *at least 30 minutes* (60 minutes for ibandronate) before ingesting food, beverage, or other medications.

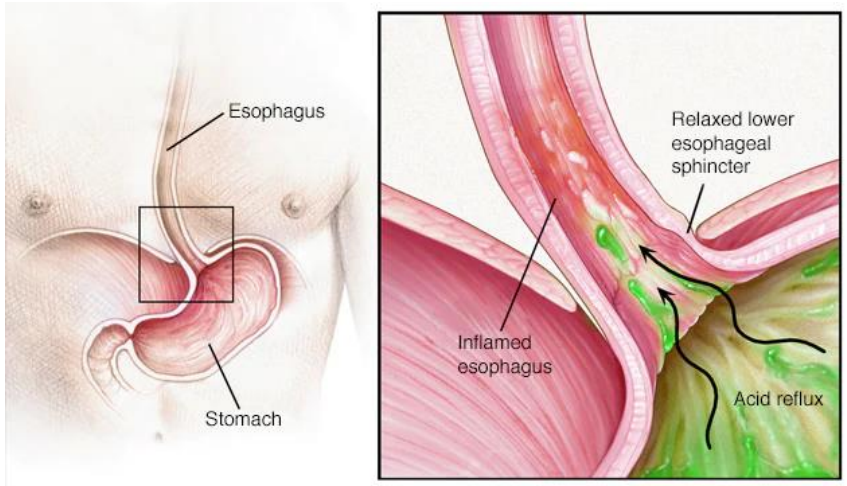
Patients **should not lie down**, but should stay **fully upright for at least 30 minutes** (60 minutes for ibandronate) after ingesting an oral bisphosphonate to prevent esophageal irritation or ulceration and to ensure appropriate bioavailability.

Prevention

With all bisphosphonates, patients should ingest *adequate calcium and vitamin D*, but **should not** take the calcium or vitamin D at the **same time** as the oral bisphosphonates because they may decrease the absorption of bisphosphonates.

Prevention

A diagnosis of GERD may **preclude** the use of oral bisphosphonate therapy for prevention of osteoporosis due to gastric irritation. **Zoledronic acid** for prevention of osteoporosis is an alternative.



Prevention

The current guidelines from the NOF and NAMS recommend pharmacologic therapy be reserved for those patients with a hip or vertebral fracture, individuals with a T-score of −2.5 or less at the femoral neck or spine once secondary causes have been excluded, and individuals with low bone mass with a 10-year probability of at least 3% risk of hip fracture or at least 20% risk of major osteoporotic fracture.

Prevention

Contraindications and Precautions

Hypocalcemia should be corrected before beginning therapy and all patients on bisphosphonates should receive adequate *calcium and vitamin D* through diet and/or supplements. Patients on loop diuretics should be monitored for hypocalcemia. Patients receiving zoledronic acid should be appropriately *hydrated*, the infusion given over no less than 15 minutes, then followed by a 10 mL of normal saline flush. To reduce the incidence of acute-phase reaction symptoms, *acetaminophen* may be given post-infusion.

Prevention

Although no dosage adjustments are recommended for patients with mild renal insufficiency, alendronate and zoledronic acid are not recommended in patients with creatinine clearance less than **35 mL/minute** and ibandronate and risedronate are not recommended in patients with creatinine clearance <30 mL/minute.

Prevention

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

Raloxifene is a benzothiophene second-generation selective estrogen receptor modulator with both agonist and antagonist action on select estrogen target tissues. Raloxifene binds to estrogen receptors (ER) resulting in estrogen **agonist** effect in *bone* and *lipid metabolism* and estrogen **antagonist** effect in *breast* and *endometrial tissue*.

Prevention

Raloxifene's agonist activity on bone tissue is believed to effect osteoclastogenesis, leading to a *reduction in bone resorption* and a decreased rate of bone turnover, increasing BMD.

In clinical trials, women who took raloxifene had an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

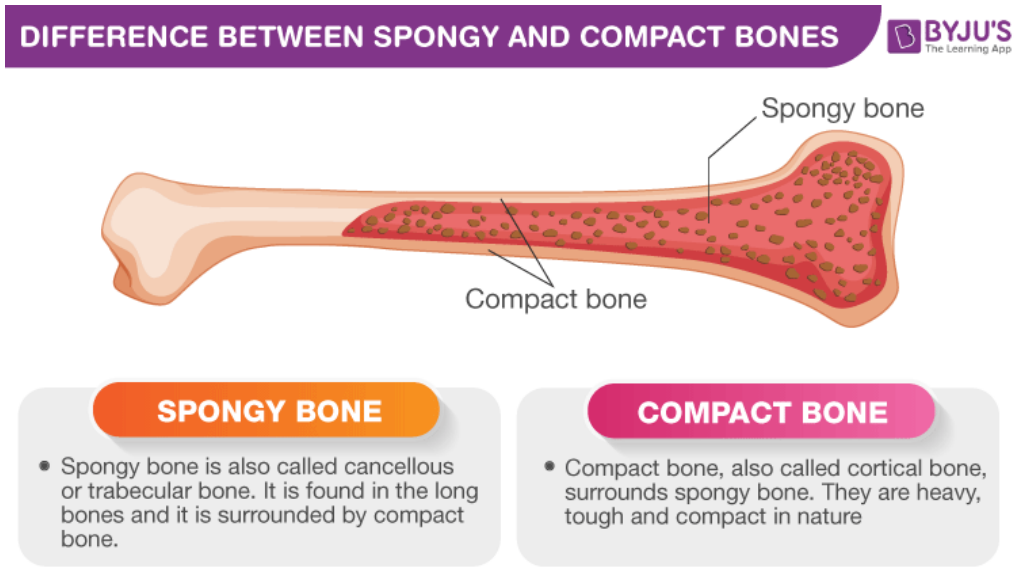
Prevention

A paradox still exists regarding how raloxifene can decrease *vertebral fractures* by up to 41% while increasing BMD by only 2% to 3%, rates that are lower than those noted for ET, EPT, or alendronate. In addition, raloxifene has **not** been observed to have a significant effect on *hip fractures* when compared to other agents.

Prevention

The anti-fracture effect of raloxifene on *vertebral* fractures may occur secondary to normalization of the high turnover rate of **cancellous** bone, which then prevents further disruption of bone microarchitecture.

This may occur through raloxifene binding at estrogen β-receptor sites that are predominantly in cancellous bone, whereas α-receptors are predominantly in cortical bone. Thus, bone type and estrogen receptors are different in the hips compared with vertebrae.



Prevention

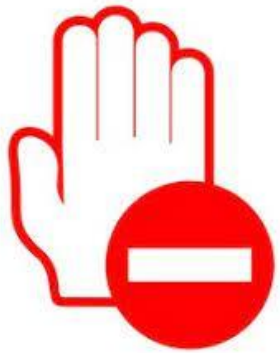
Raloxifene 60 mg once daily can be taken without regard for food. *Adverse effects* of raloxifene include an increased risk for *venous thromboembolic disease*, flu syndrome, headache, hot flashes, nausea, diarrhea, flatulence, gastroenteritis, leg cramps, peripheral edema, arthralgia, neuralgia, sinusitis, bronchitis, rash, sweating, and conjunctivitis.

Prevention

Contraindications and Potential Drug Interactions

Raloxifene carries a boxed warning and is **contraindicated** in patients with active venous thromboembolism or a past history of venous thromboembolism due to increased risk. Raloxifene is **contraindicated** in women who are pregnant, plan to become pregnant, and those nursing.

Raloxifene should be used with caution during periods of *prolonged immobilization*, in patients with a history or risk of stroke, moderate or severe renal impairment, and in patients with hepatic impairment.



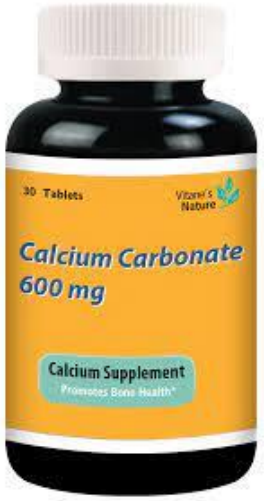
Treatment

A treatment plan for **patients with fractures** should be aimed at *preventing further bone loss* and minimizing falls, which could lead to further fractures. It is important to continue *calcium and vitamin D* in the diet and maximize the physical function by incorporating *exercise* in the treatment plan.

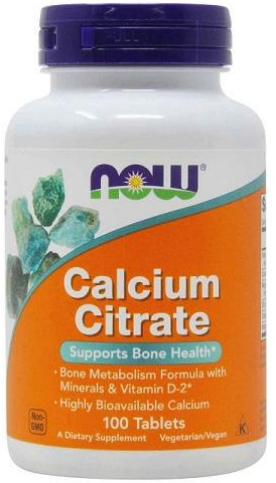
Calcium and vitamin D supplementation in combination can improve bone density as well as prevent incident fractures in postmenopausal women with osteoporosis. It is difficult, however, to find **evidence** to support the benefit of supplements for treatment of secondary prevention of fracture in older patients diagnosed with osteoporosis.

Treatment

Maintaining serum 25-OH-D levels above 30 ng/mL (75 nmol/L) is an important goal as low levels of *vitamin D* are associated with an increased risk of **falling**.



There is some controversy on whether *gastric acid secretion* is decreased with *aging* and if patients who are older should take calcium citrate instead of calcium carbonate. **Calcium carbonate** supplements are the form most often associated with **constipation**, which can be problematic as gastric motility is decreased with aging. Calcium citrate should be used over calcium carbonate in patients with *achlorhydria*, a condition common in the elderly, and in those patients who *complain of constipation*.



Treatment

EXERCISE AND FALL PREVENTION

Falls are common among older adults and the leading cause of fractures and injury, both fatal and nonfatal.

Any patient who presents to a clinician after a fall should have a *risk assessment* as well. Patients at higher risk of falling include those with deficits in gait and balance, foot problems, impairment of vision, cardiovascular disease, postural hypotension, and vitamin D deficiency. *Removal of contributing factors* and treating underlying medical conditions with the fewest medications possible can reduce the risk of falling.

Treatment

The **prevention of falls** also includes maintaining a safe environment, reducing tripping hazards, adding handrails inside and outside the tub or shower and next to the toilet, and improving the lighting in the home.

Treatment

PHARMACOTHERAPY

Pharmacologic treatment is indicated in patients who have experienced a hip or vertebral fracture, in those with T-scores < −2.5 at the femoral neck, total hip, or lumbar spine, and in postmenopausal women and men age 50 and older with low bone mass and high risk of fracture.

Agents *approved for treatment* of osteoporosis include bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), calcitonin, denosumab, estrogen, raloxifene, and teriparatide.

Treatment

Estrogen

Conjugated estrogen therapy has positive effects on BMD and fracture rates, but is **no longer** recommended for the treatment of osteoporosis.

Treatment

Selective Estrogen Receptor Modulators

Raloxifene is the *only SERM* approved in the United States that is indicated for the treatment and prevention of osteoporosis in postmenopausal women. The safety and efficacy of raloxifene have been studied in a randomized controlled trial up to **7 years**.

Treatment

Bisphosphonates

Bisphosphonates, such as alendronate, risedronate, ibandronate, or zoledronic acid, can be used as an alternative to raloxifene to prevent fractures due to osteoporosis.

Treatment

Calcitonin

Calcitonin decreases bone resorption and bone turnover. *Synthetic calcitonin* made from salmon is 40 to 50 times more potent than human calcitonin. A nasal spray and an injectable formulation are available and indicated for the treatment of osteoporosis in women who have been postmenopausal for at least 5 years.

Calcitonin is only recommended for the treatment of osteoporosis when alternatives are not suitable and can be considered **third-line** treatment. Fracture reduction has **not** been shown in quality clinical trials.

Treatment

Common nasal symptoms from nasal administration include rhinitis, nasal sores, irritation, itching, sinusitis, and epistaxis.

Local skin reactions (10%) are common with *injectable* calcitonin. Nausea with or without vomiting (10%) and flushing (2%–5%) can occur at initiation of therapy, but subsides over time. Other adverse effects include arthralgia, headache, and back pain. More severe adverse effects associated with calcitonin salmon include serious hypersensitivity, hypocalcemia, and malignancy.

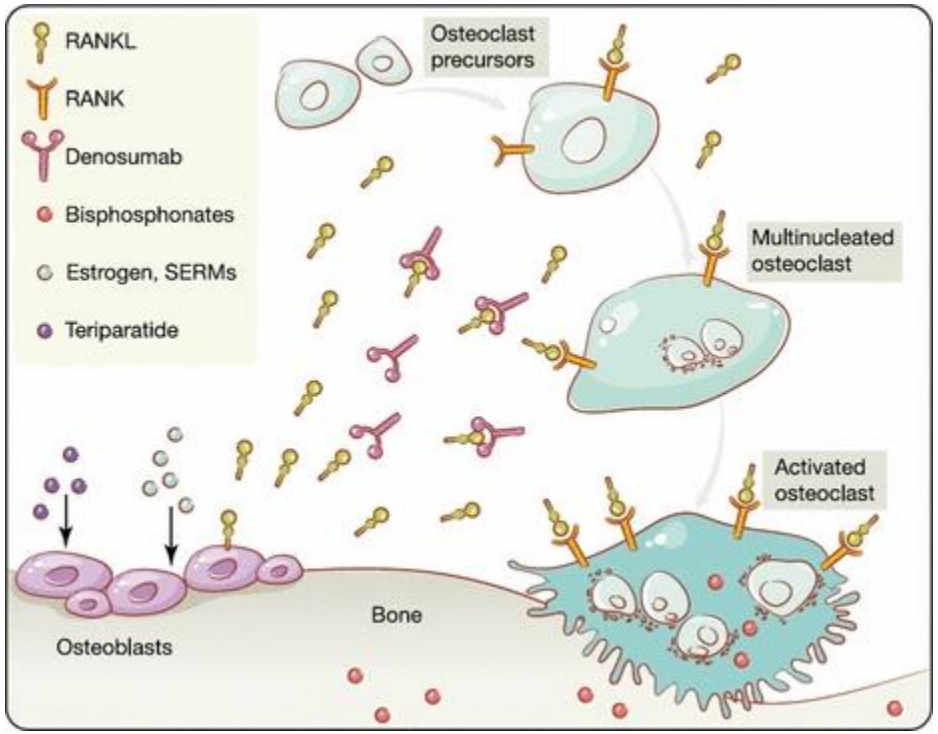
Treatment

Injectable calcitonin should be **refrigerated** when not in use and nasal spray refrigerated until it is opened for use; thereafter, it is stable for 30 days at room temperature. Calcitonin nasal spray should be used in *alternate nostrils* daily.

Treatment

Denosumab

Denosumab is a human monoclonal antibody that binds to RANKL, a regulator of bone-resorbing osteoclasts. Denosumab is administered by *subcutaneous* injection **every 6 months** and inhibits bone turnover with a rapid onset. Denosumab significantly increases BMD in the lumbar spine, total hip, and at the femoral neck compared to placebo. This effect **dissipates quickly** and BMD returns to approximately *baseline levels* within 12 months of discontinuation.



Treatment

Common adverse reactions include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. *Serious infections* including cellulitis can occur when taking denosumab as well as skin rash and eczema.

There is a risk of **hypocalcemia** with treatment. Adequate supplementation of *calcium and vitamin D*, at least 1,000 mg of calcium and 400 IU of vitamin D daily, is recommended. Hypocalcemia must be corrected before the initiation of treatment. Serious hypersensitivity reactions, pancreatitis, osteonecrosis of the jaw (ONJ), and atypical femur fractures have all been reported.

Treatment

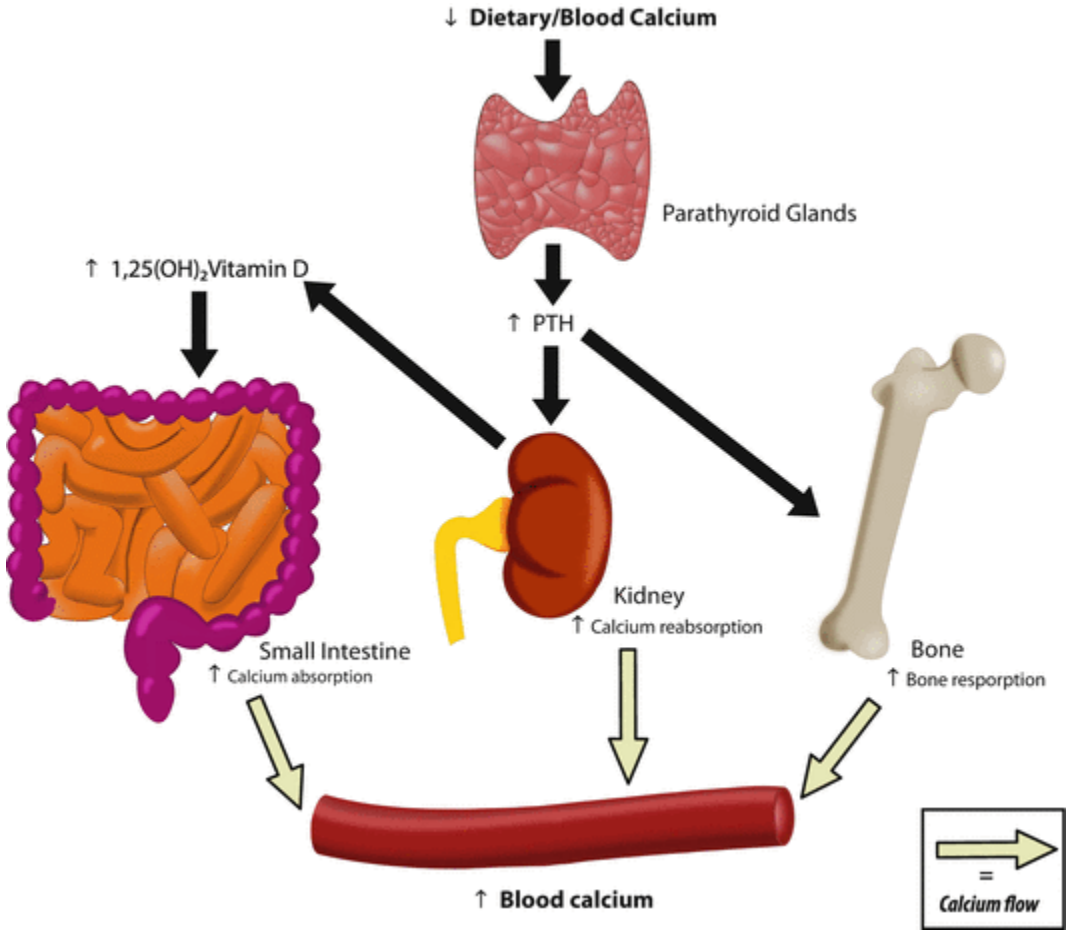
Denosumab is available as prefilled syringes that should be stored in the refrigerator at 2°C to 8°C (36°F–46°F). It should be left out and brought to room temperature for administration. It is recommended that a healthcare provider administers denosumab by subcutaneous injection in the upper arm, upper thigh, or abdomen.

Treatment

Parathyroid Hormone

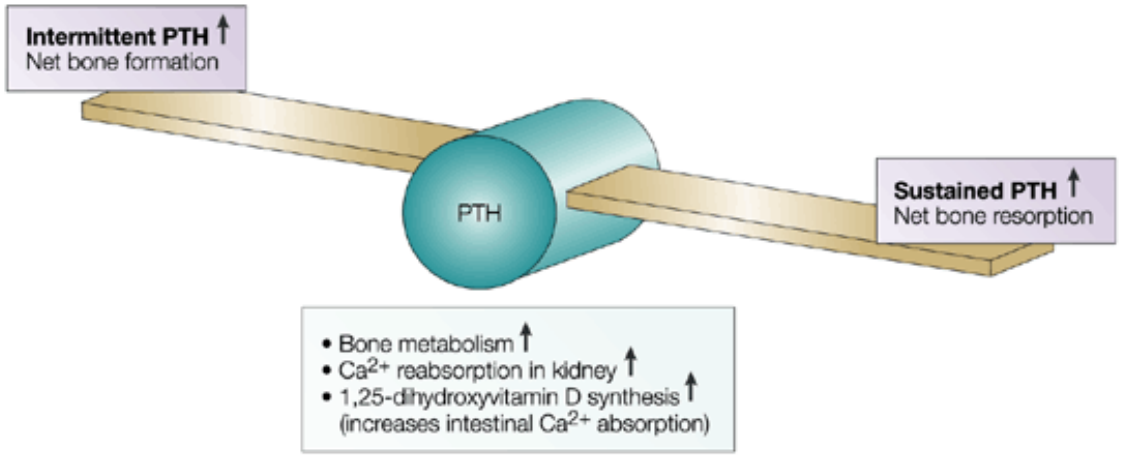
Endogenous parathyroid hormone (PTH) regulates the level of calcium in the blood. Even a small decrease in calcium will cause secretion of PTH.

It acts on the *kidneys* to conserve calcium and stimulate the production of *calcitriol*, which increases the absorption of calcium. PTH stimulates bone formation and bone resorption, but also *increases the movement of calcium from the bone* to the blood.



Treatment

Excessive PTH causes bone *breakdown* by osteoclasts and has been shown to contribute to bone loss and bone fragility. A **controlled intermittent injection**, however, promotes bone formation, increasing BMD and bone size.

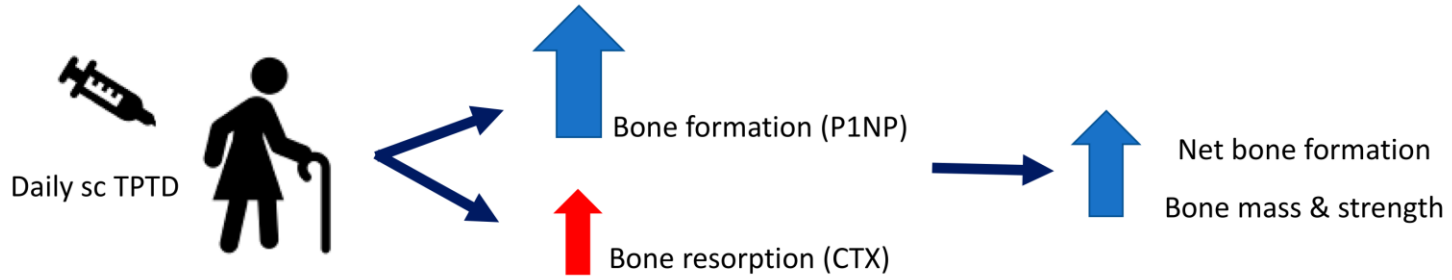


Treatment

Teriparatide is a human recombinant fragment of the first 34 amino acids of parathyroid hormone (PTH 1-34), which produce most of its chief biologic effects. It is available as a multi-dose pen, given as a daily 20 mcg subcutaneous injection.

Treatment

Early clinical trials in humans were *stopped prematurely* because **animal** data showed increased incidence of **osteosarcoma** at high doses and long duration. A boxed warning for the potential risk of osteosarcoma appears in the manufacturer's package information and a medication guide is required to be dispensed with teriparatide.



Treatment

Teriparatide has a *unique mechanism* of action that makes it attractive to **combine** with other medications to treat osteoporosis. Teriparatide may have a slight benefit in combination with bisphosphonates and more significant effects when combined with denosumab, but more information is needed to determine the effect on fracture risk.

Teriparatide has been used to treat and promote **healing** of bisphosphonate- or denosumab-induced *osteonecrosis of the jaw*.

Treatment

Initial administration of teriparatide should be given when the patient can sit or lie down as **orthostatic hypotension** may occur with the initial doses. Teriparatide pens are stable for up to 28 days, including the first injection. The remaining medication should be discarded after 28 days. Teriparatide should be stored under refrigeration at 2°C to 8°C (36°F–46°F) and injected immediately on removal from refrigeration. After use, the pen should be recapped and protected from light.

Safety and efficacy with teriparatide is limited beyond 2 years and therapy is **not recommended** for **longer than 2 years** at this time.

Treatment

Adverse effects reported include *hypercalcemia*, leg cramps, nausea, and dizziness. *Orthostatic hypotension* may occur within **4 hours of administration** and spontaneously resolves after a few minutes to hours for the first several doses. Patients should immediately sit or lie down if symptoms occur.