Agents that Affect Bone & Mineral Homeostasis

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Reference

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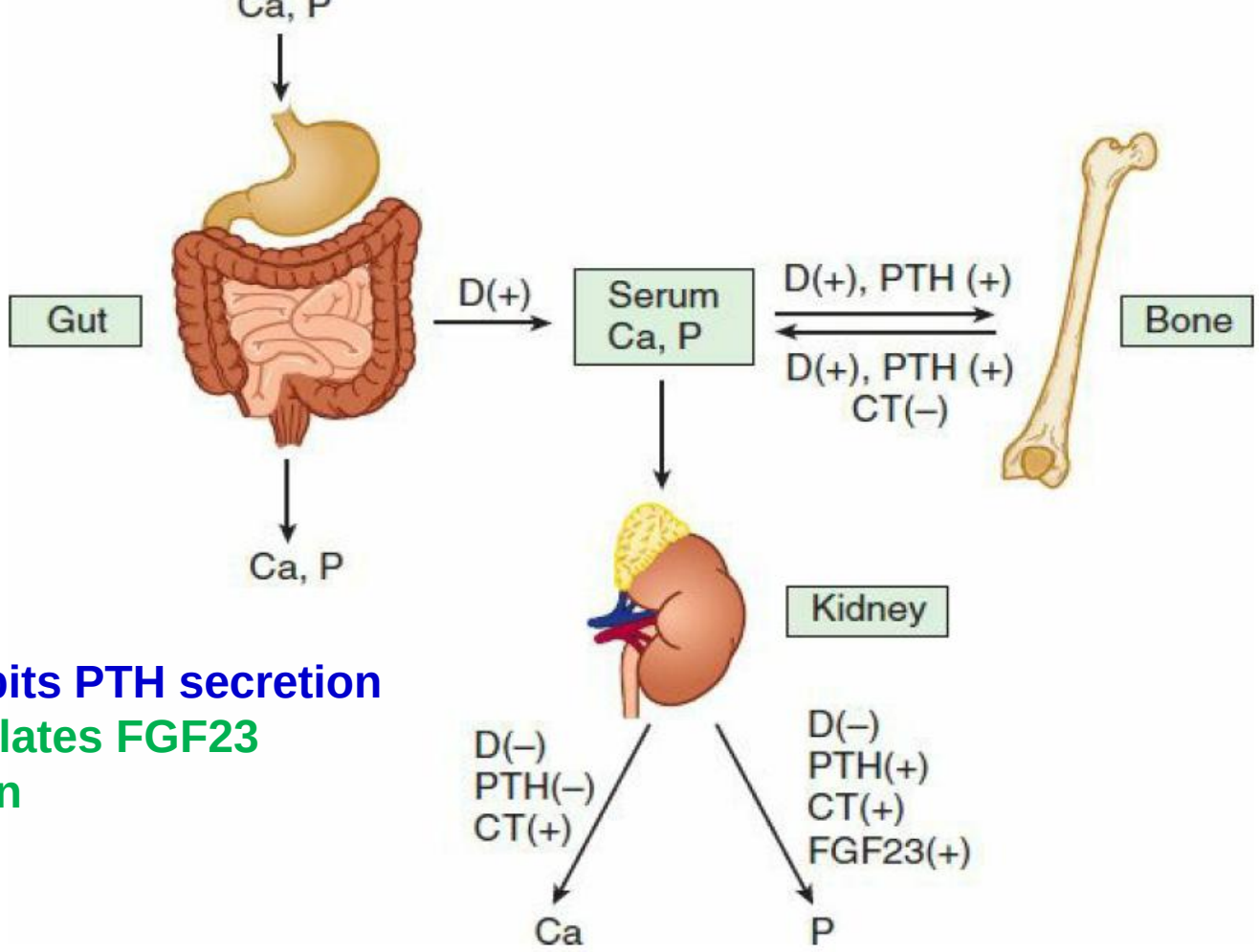
Agents that Affect Bone & Mineral Homeostasis

- **Calcium and phosphate are the major mineral constituents of bone.**
- **They are also two of the most important minerals for general cellular function.**
- **Principal regulators of calcium and phosphate homeostasis: Parathyroid hormone, fibroblast growth factor 23 (FGF23) & vitamin D via its active metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).**



Vit D inhibits PTH secretion and stimulates FGF23 production

FIGURE 42–1 Mechanisms contributing to bone mineral homeostasis. Serum calcium (Ca) and phosphorus (P) concentrations are controlled principally by three hormones, 1,25-dihydroxyvitamin D (D), fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on renal excretion. PTH and $1,25(OH)_2D$ increase the input of calcium and phosphorus from bone into the serum and stimulate bone formation. $1,25(OH)_2D$ also increases calcium and phosphate absorption from the gut. In the kidney, $1,25(OH)_2D$ decreases excretion of both calcium and phosphorus, whereas PTH reduces calcium but increases phosphorus excretion. FGF23 stimulates renal excretion of phosphate. Calcitonin (CT) is a less critical regulator of calcium homeostasis, but in pharmacologic concentrations can reduce serum calcium and phosphorus by inhibiting bone resorption and stimulating their renal excretion. Feedback may alter the effects shown; for example, $1,25(OH)_2D$ increases urinary calcium excretion indirectly through increased calcium absorption from the gut and inhibition of PTH secretion and may increase urinary phosphate excretion because of increased phosphate absorption from the gut and stimulation of FGF23 production.

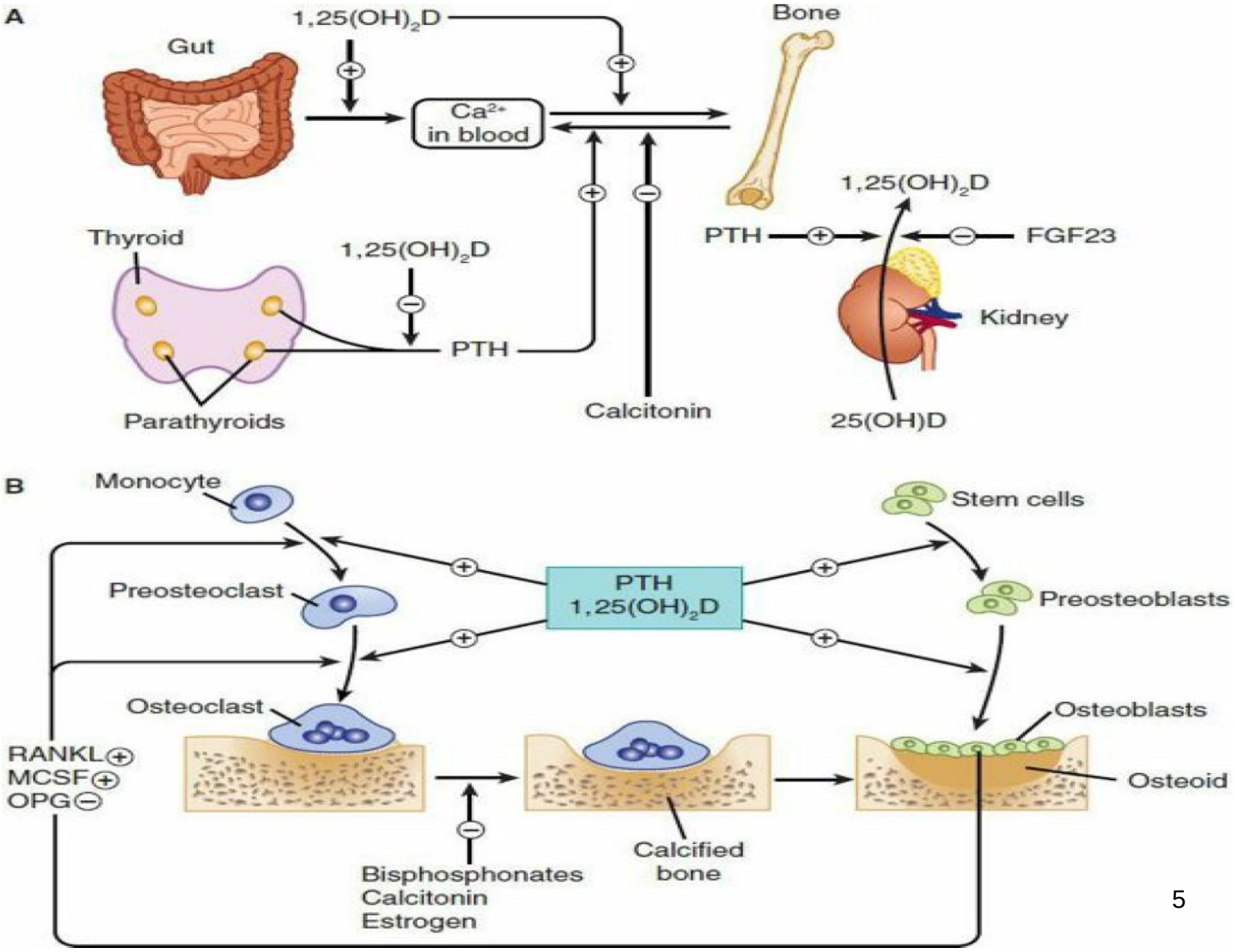

A
1,25(OH)2D
Gut
Ca2+ in blood
Bone
1,25(OH)2D
PTH
FGF23
Kidney
Thyroid
1,25(OH)2D
PTH
Parathyroids
Calcitonin
25(OH)D
B
Monocyte
Stem cells
Preosteoclast
PTH
1,25(OH)2D
Preosteoblasts
Osteoclast
Osteoblasts
RANKL
MCSF
OPG
Osteoid
Calcified bone
Bisphosphonates
Calcitonin
Estrogen

FIGURE 42–2 The hormonal interactions controlling bone mineral homeostasis. In the body **(A)**, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) is produced by the kidney under the control of parathyroid hormone (PTH), which stimulates its production, and fibroblast growth factor 23 (FGF23), which inhibits its production. $1,25(OH)_2D$ in turn inhibits the production of PTH by the parathyroid glands and stimulates FGF23 release from bone. $1,25(OH)_2D$ is the principal regulator of intestinal calcium and phosphate absorption. At the level of the bone **(B)**, both PTH and $1,25(OH)_2D$ regulate bone formation and resorption, with each capable of stimulating both processes. This is accomplished by their stimulation of preosteoblast proliferation and differentiation into osteoblasts, the bone-forming cell. PTH also stimulates osteoblast formation indirectly by inhibiting the osteocyte's production of sclerostin, a protein that blocks osteoblast proliferation by inhibiting the wnt pathway (not shown). PTH and $1,25(OH)_2D$ stimulate the expression of RANKL by the osteoblast, which, with MCSF, stimulates the differentiation and subsequent activation of osteoclasts, the bone-resorbing cell. OPG blocks RANKL action, and may be inhibited by PTH and $1,25(OH)_2D$. FGF23 in excess leads to osteomalacia indirectly by inhibiting $1,25(OH)_2D$ production and lowering phosphate levels. MCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, ligand for receptor for activation of nuclear factor-κB.

PTH also stimulates osteoblast formation indirectly by inhibiting osteocyte's production of sclerostin which blocks osteoblast proliferation.

PTH and D stimulate the expression of RANKL by osteoblasts which stimulates differentiation and activation of osteoclasts.

OPG (osteoprotegerin) blocks RANKL action. (may be inhibited by PTH and D).

FGF23 in excess inhibit D production and lower P levels → osteomalacia.

Agents that Affect Bone & Mineral Homeostasis

- **Secondary regulators:** calcitonin, prolactin, growth hormone, insulin, thyroid hormone, glucocorticoids, and sex steroids.
- Calcium and phosphate themselves, other ions such as sodium and fluoride, and a variety of drugs (bisphosphonates, plicamycin, and diuretics) also alter calcium and phosphate homeostasis.

Parathyroid Hormone

- **Parathyroid hormone (PTH) is a single-chain peptide hormone composed of 84 amino acids.**
- **Calcium limits the production of PTH by:**

1. **Calcium-sensitive protease cleaves the intact hormone into fragments.**
2. **Calcium-sensing receptor (CaSR) is stimulated by calcium, to reduce PTH production and secretion.**

Parathyroid Hormone

- **The parathyroid gland vitamin D receptor (VDR) activation, and the enzyme CYP27B1, that produces $1,25(OH)_2D$, suppress PTH production.**
- **$1,25(OH)_2D$ also <u>induces</u> the CaSR, making the parathyroid gland more sensitive to suppression by calcium.**

Parathyroid Hormone

- **Biologic activity resides in the amino terminal region of PTH such that synthetic PTH 1-34 (teriparatide) is fully active.**
- **Loss of the first two amino terminal amino acids eliminates most biologic activity.**
- **PTH regulates calcium and phosphate flux across cellular membranes in bone and kidney, resulting in increased serum calcium and decreased serum phosphate.**

Parathyroid Hormone

- **In bone, PTH increases the activity and number of osteoclasts (the cells responsible for bone resorption) indirectly by acting on the osteoblast (the bone-forming cell) to induce membrane-bound and secreted soluble forms of a protein called RANK (receptor for activation of nuclear factor κB) ligand (RANKL).**

Parathyroid Hormone

- **RANKL increases both the number and activity of osteoclasts.**
- **Denosumab, a monoclonal antibody that inhibits the action of RANKL, is used in the treatment of excess bone resorption in patients with osteoporosis and certain cancers.**

Parathyroid Hormone

- **PTH also inhibits the production and secretion of sclerostin (which blocks osteoblast proliferation) from osteocytes.**
- **Thus, PTH indirectly increases proliferation of osteoblasts, the cells responsible for bone formation.**

Parathyroid Hormone

- Although both bone resorption and bone formation are enhanced by PTH, the net effect of excess endogenous PTH is to increase bone resorption.
- Administration of exogenous PTH in low and intermittent doses increases bone formation without first stimulating bone resorption.
- This has led to a recombinant PTH 1-34 (teriparatide) for the treatment of osteoporosis.

Parathyroid Hormone

Teriparatide:

1. **Given daily by subcutaneous injection.**
2. **It stimulates normal bone formation.**
3. **It reduces incidence of fractures.**

- **Adequate intake of calcium and vitamin D must be maintained.**

Parathyroid Hormone

- **In the kidney, PTH increases tubular reabsorption of calcium and magnesium but reduces reabsorption of phosphate, amino acids, bicarbonate, sodium, chloride, and sulfate.**
- **PTH stimulates $1,25(OH)_2D$ production by the kidney.**

Vitamin D

- **Vitamin D is a secosteroid produced in the skin from 7-dehydrocholesterol under the influence of ultraviolet radiation.**
- **Vitamin D is also found in certain foods and is used to supplement dairy products and other foods.**
- **Both the natural form (vitamin D_3, cholecalciferol) and the plant-derived form (vitamin D_2, ergocalciferol) are present in the diet.**

Vitamin D

- **Vitamin D is first hydroxylated in the liver and other tissues to form 25(OH)D (calcifediol), by a number of enzymes, of which CYP2R1 is the most important.**
- **This metabolite is further converted in the kidney to 1,25$(OH)_2$D (calcitriol) by the enzymes CYP27B1.**

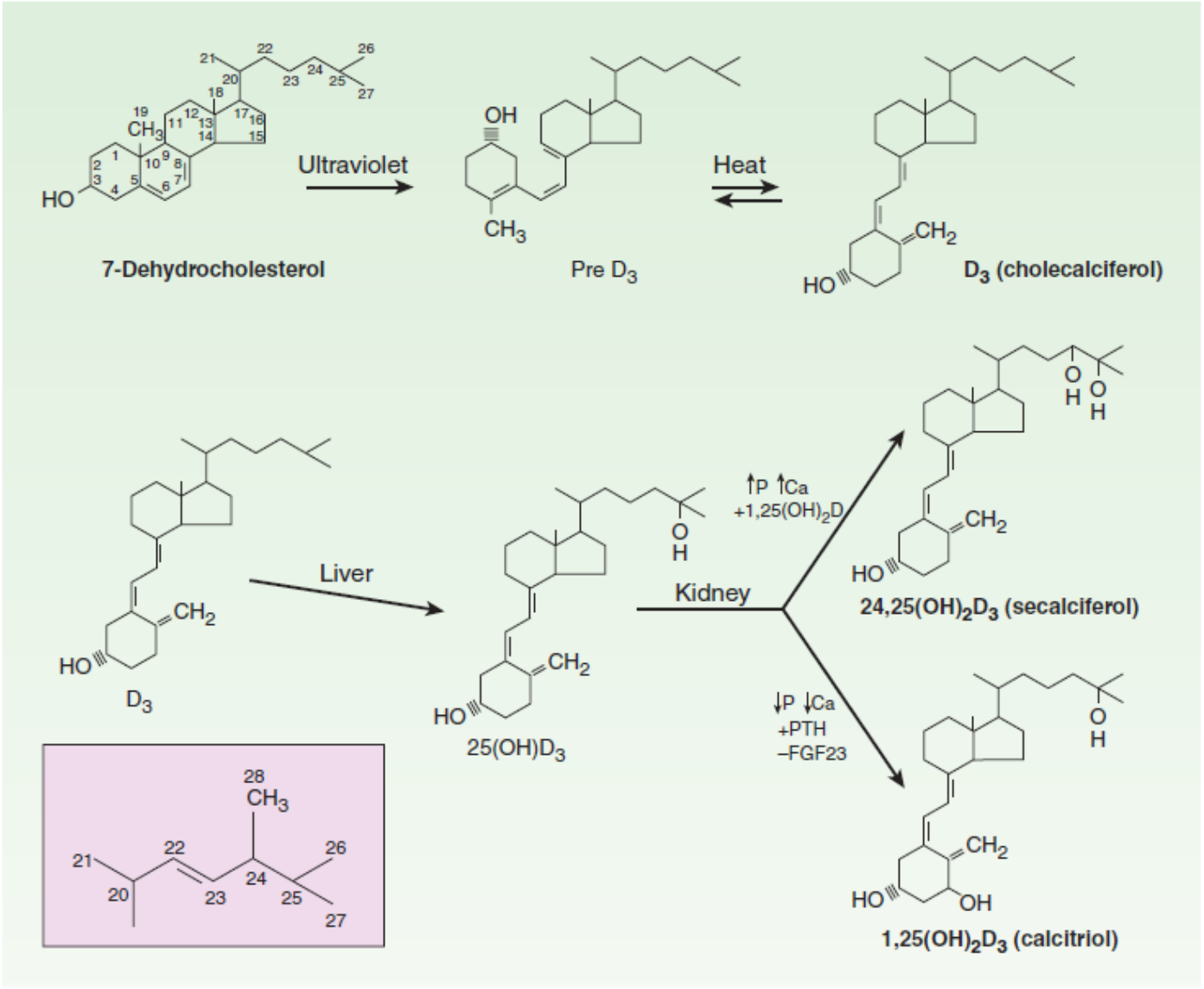


FIGURE 42–3 Conversion of 7-dehydrocholesterol to vitamin D_3 and metabolism of D_3 to 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) and 24,25-dihydroxyvitamin D_3 ($24,25[OH]_2D_3$). Control of the latter step is exerted primarily at the level of the kidney, where low serum phosphorus, low serum calcium, and high parathyroid hormone favor the production of $1,25(OH)_2D_3$, whereas fibroblast growth factor 23 inhibits its production. The inset shows the side chain for ergosterol. Ergosterol undergoes similar transformation to vitamin D_2 (ergocalciferol), which, in turn, is metabolized to 25-hydroxyvitamin D_2, 1,25-dihydroxyvitamin D_2, and 24,25-dihydroxyvitamin D_2. In humans, corresponding D_2 and D_3 derivatives have equivalent effects although they differ in pharmacokinetics.

Vitamin D

- **The regulation of vitamin D metabolism is complex, involving calcium, phosphate, and a variety of hormones, the most important of which are PTH, which stimulates, and FGF23, which inhibits the production of $1,25(OH)_2D$ by the kidney.**

Vitamin D

- **Vitamin D and its metabolites circulate in plasma tightly bound to the DBP, an α-globulin.**
- **Excess vitamin D is stored in adipose tissue.**
- **$1,25(OH)_2D$ is well established as the most potent stimulant of intestinal calcium and phosphate transport and bone resorption.**

Vitamin D

Other analogs:

1. **Calcipotriene: for psoriasis.**
2. **Doxercalciferol & paricalcitol: for secondary hyperparathyroidism in patients with chronic kidney disease.**
3. **Eldecalcitol is in phase 3 clinical trials for the treatment of osteoporosis.**
4. **Other analogs are being investigated for the treatment of various malignancies.**

TABLE 42–1 Vitamin D and its major metabolites and analogs.

Chemical and Generic Names	Abbreviation
Vitamin D_3; cholecalciferol	D_3
Vitamin D_2; ergocalciferol	D_2
25-Hydroxyvitamin D_3; calcifediol	$25(OH)D_3$
1,25-Dihydroxyvitamin D_3; calcitriol	$1,25(OH)_2D_3$ *
24,25-Dihydroxyvitamin D_3; secalciferol	$24,25(OH)_2D_3$
Dihydrotachysterol	DHT
Calcipotriene (calcipotriol)	None
1α-Hydroxyvitamin D_2; doxercalciferol	$1\alpha(OH)D_2$
19-nor-1,25-Dihydroxyvitamin D_2; paricalcitol	19-nor-$1,25(OH)D_2$

Vitamin D

- **$1,25(OH)_2D$ can induce RANKL in osteoblasts and proteins such as osteocalcin, which may regulate the mineralization process.**
- **Specific receptors for $1,25(OH)_2D$ (VDR) exist in nearly all tissues, not just intestine, bone, and kidney.**
- **There is a need to develop analogs of $1,25(OH)_2D$ that will target these non-classic tissues without increasing serum calcium.**

Vitamin D

- **These nonclassic actions include regulation of the secretion of PTH, insulin, and renin; dendritic cell as well as T-cell differentiation; and proliferation and differentiation of a number of cancer cells.**
- **Thus, the clinical utility of $1,25(OH)_2D$ and its analogs is expanding.**

Vitamin D

- **The reduced intestinal calcium transport associated with osteoporosis is counteracted by vitamin D therapy with calcium supplementation.**
- **Calcitriol ($1,25(OH)_2D$) and its analog $1\alpha(OH)D_3$ increase bone mass and reduce fractures.**

Fibroblast Growth Factor 23

- **FGF23 is a single-chain protein with 251 amino acids.**
- **It inhibits $1,25(OH)_2D$ production and phosphate reabsorption in the kidney, and can lead to both hypophosphatemia and low levels of $1,25(OH)_2D$.**
- **Osteoblasts and osteocytes in bone appear to be its primary site of production.**

Fibroblast Growth Factor 23

- **FGF23 requires *O-glycosylation for its secretion, mediated by the glycosyl* transferase GALNT3.**
- **Mutations in GALNT3 result in abnormal deposition of calcium phosphate in periarticular tissues (tumoral calcinosis) with elevated phosphate and 1,25$(OH)_2$D.**
- **FGF23 is normally inactivated by cleavage at amino acids 176–179. Mutations in this site lead to excess FGF23, the underlying problem in autosomal dominant hypophosphatemic rickets.**

Fibroblast Growth Factor 23

- **FGF23 binds to FGF receptors 1 and 3c in the presence of an accessory receptor (Klotho).**
- **Both the accessory receptor and the FGF23 receptor must be present for signaling.**
- **Mutations in Klotho disrupt FGF23 signaling, resulting in elevated phosphate and $1,25(OH)_2D$ levels.**

Fibroblast Growth Factor 23

- **FGF23 production is stimulated by $1,25(OH)_2D$ and phosphate and directly or indirectly inhibited by the dentin matrix protein DMP1 found in osteocytes.**
- **Mutations in DMP1 lead to increased FGF23 levels and osteomalacia.**

Interaction of PTH, FGF23, & Vitamin D

- **The net effect of PTH is to raise serum calcium and reduce serum phosphate.**
- **The net effect of FGF23 is to decrease serum phosphate.**
- **The net effect of vitamin D is to raise both.**

TABLE 42–2 Actions of parathyroid hormone (PTH), vitamin D, and FGF23 on gut, bone, and kidney.

	PTH	Vitamin D	FGF23
Intestine	Increased calcium and phosphate absorption (by increased $1,25(OH)_2D$ production)	Increased calcium and phosphate absorption by $1,25(OH)_2D$	Decreased calcium and phosphate absorption by decreased $1,25(OH)_2$ production
Kidney	Decreased calcium excretion, increased phosphate excretion	Calcium and phosphate excretion may be decreased by 25(OH)D and $1,25(OH)_2D$[1]	Increased phosphate excretion
Bone	Calcium and phosphate resorption increased by high doses. Low doses may increase bone formation.	Increased calcium and phosphate resorption by $1,25(OH)_2D$; bone formation may be increased by $1,25(OH)_2D$ and $24,25(OH)_2D$	Decreased mineralization due to hypophosphatemia and low 1,25(OH)2D levels, but may have a direct action on bone as well.
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased	Decreased serum phosphate

[1]Direct effect. Vitamin D also indirectly increases urine calcium owing to increased calcium absorption from the intestine and decreased PTH.

Interaction of PTH, FGF23, & Vitamin D

- **Calcium regulates PTH secretion.**
- **It binds to a Gq protein-coupled receptor called the calcium-sensing receptor (CaSR) that employs the phosphoinositide second messenger system to link changes in the extracellular calcium concentration to changes in the intracellular free calcium.**

Interaction of PTH, FGF23, & Vitamin D

- As serum calcium levels rise and activate this receptor, intracellular calcium levels increase and inhibit PTH secretion.
- This is the opposite of the effect in other tissues (β cell of the pancreas) in which calcium stimulates secretion.

Interaction of PTH, FGF23, & Vitamin D

- **Phosphate regulates PTH secretion directly and indirectly by forming complexes with calcium in the serum.**
- **Because it is the ionized free concentration of extracellular calcium that is detected by the parathyroid gland, increases in serum phosphate levels reduce the ionized calcium, leading to enhanced PTH secretion.**

Interaction of PTH, FGF23, & Vitamin D

- **Both calcium and phosphate at high levels reduce the amount of $1,25(OH)_2D$ produced by the kidney.**
- **High serum phosphate works directly and indirectly by increasing FGF23 levels.**
- **$1,25(OH)_2D$ directly inhibits PTH secretion (independent of its effect on serum calcium) by an effect on PTH gene transcription. This provides a negative feedback.**

Interaction of PTH, FGF23, & Vitamin D

- In patients with chronic renal failure who are $1,25(OH)_2D$ deficient, loss of this $1,25(OH)_2D$-mediated feedback loop coupled with impaired phosphate excretion and intestinal calcium absorption lead to secondary hyperparathyroidism.
- This explains the role of the calcitriol analogs in the management of secondary hyperparathyroidism of chronic kidney disease.

Interaction of PTH, FGF23, & Vitamin D

- **$1,25(OH)_2D$ also stimulates the production of FGF23.**
- **This completes the negative feedback loop in that FGF23 inhibits $1,25(OH)_2D$ production while promoting hypophosphatemia, which in turn inhibits FGF23 production and stimulates $1,25(OH)_2D$ production.**

Secondary Hormonal Regulators of Bone Mineral Homeostasis

Secondary Hormonal Regulators of Bone Mineral Homeostasis

- **A number of hormones modulate the actions of PTH, FGF23, and vitamin D in regulating bone mineral homeostasis.**
- **The physiologic impact of such secondary regulation on bone mineral homeostasis is minor.**
- **In pharmacologic amounts, they may have actions that are useful therapeutically.**

Calcitonin

- **Calcitonin secreted by the parafollicular cells of the thyroid is a single-chain peptide hormone with 32 amino acids and a molecular weight of 3600.**
- **Human calcitonin monomer has a half-life of ~ 10 minutes. Salmon calcitonin has a longer half-life of 40–50 minutes, making it more attractive as a therapeutic agent.**
- **Clearance mainly by the kidney by metabolism; little intact calcitonin appears in the urine.**

Calcitonin

- **The principal effects of calcitonin are to lower serum calcium and phosphate by actions on bone and kidney.**
- **Calcitonin inhibits osteoclastic bone resorption. With time both formation and resorption of bone are reduced.**
- **In the kidney, calcitonin reduces both calcium and phosphate reabsorption as well as reabsorption of sodium, potassium, and magnesium.**

Calcitonin

- **Tissues other than bone and kidney are also affected by calcitonin.**
- **Calcitonin in pharmacologic amounts decreases gastrin secretion and reduces gastric acid output while increasing secretion of sodium, potassium, chloride, and water in the gut.**
- **Pentagastrin is a potent stimulator of calcitonin secretion (as is hypercalcemia), suggesting a possible physiologic relationship between gastrin and calcitonin.**

Calcitonin

- **In the adult human, no problem develops in cases of calcitonin deficiency (thyroidectomy) or excess (medullary carcinoma of the thyroid).**
- **The ability of calcitonin to block bone resorption and lower serum calcium makes it a useful drug for the treatment of Paget's disease, hypercalcemia, and osteoporosis, but is less efficacious than other available agents.**

Calcitonin

- **It increases bone mass and reduces spine fractures, but is less effective than bisphosphonates and teriparatide.**

Glucocorticoids

- Glucocorticoid hormones alter bone mineral homeostasis by antagonizing vitamin D-stimulated intestinal calcium transport, stimulating renal calcium excretion, and blocking bone formation.
- They are useful in reversing the hypercalcemia associated with lymphomas and granulomatous diseases such as sarcoidosis (in which unregulated ectopic production of $1,25[OH]_2D$ occurs) or in cases of vitamin D intoxication.

Glucocorticoids

- **Prolonged administration of glucocorticoids is a common cause of osteoporosis in adults and can cause stunted skeletal development in children.**

Estrogens

- **Can prevent accelerated bone loss during the immediate postmenopausal period, and at least transiently increase bone in the postmenopausal woman.**
- **Reduce the bone-resorping action of PTH.**
- **Increase 1,25[OH]$_2$D level in blood, which may result from decreased serum calcium and phosphate and increased PTH.**

Estrogens

- **Estrogen receptors have been found in bone, and estrogen has direct effects on bone remodeling.**
- **Men lacking estrogen receptors, or those unable to produce estrogen because of aromatase deficiency, develop marked osteopenia and failure to close epiphysis (case reports).**

Estrogens

- **Main role is in prevention and treatment of postmenopausal osteoporosis.**
- **Estrogen therapy has been shown to be associated with endometrial and breast cancer in postmenopausal women and without decreased incidence of cardiovascular disease.**

Estrogens

- **Selective estrogen receptor modulators (SERMs), such as Raloxifene, maintain the benefit to bone without increased risk of breast and uterine cancer, and cardiovascular risk.**
- **It may even decrease the risk of breast cancer.**
- **It is not as effective as estrogen in increasing bone density.**

Estrogens

- **Raloxifene may protect against spine fractures but not those of the hip (bisphosphonates and teriparatide protect against both).**
- **It does not prevent hot flushes and imposes the same increased risk of thrombophlebitis as estrogen.**

Nonhormonal Agents Affecting Bone Mineral Homeostasis

1. Bisphosphonates
2. Calcimimetics
3. Plicamycin (Mithramycin)
4. Thiazides

Bisphosphonates

- **Are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond.**
- **Drugs available for clinical use include:**

  Etidronate, Pamidronate, Alendronate, Risedronate, Tiludronate, Ibandronate, Zoledronate.
- **They retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system.**

Bisphosphonates

- They localize to regions of bone resorption and so exert their greatest effects on osteoclasts.

Pharmacokinetics:

- Absorption after oral administration is poor (~ 10%).
- Food reduces absorption.
- Half of the absorbed drug accumulates in bone, and the rest is excreted unchanged in urine. Reduce dose in renal dysfunction.

Bisphosphonates

- **The portion retained in bone stay there for months, depending on the turnover of bone itself.**

Pharmacodynamics:

- **They are potent inhibitors of bone resorption.**
- **They increase bone mineral density and reduce the risk of fractures in the hip, spine and other locations**

Bisphosphonates

- They inhibit 1,25$[OH]_2$D production.
- They inhibit intestinal calcium transport.
- They Inhibit bone cell glycolysis.
- They Inhibit bone cell growth.
- They produce changes in acid and alkaline phosphatase activity.
- They are effective in men as well as women and for various forms of osteoporosis.

Bisphosphonates

- **Can be used daily (alendronate, risedronate, ibandronate), weekly (alendronate, risedronate) or monthly (ibandronate).**

Bisphosphonates

- **The amino bisphosphonates, alendronate, inhibit farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that appears to be critical for osteoclast survival.**
- **[statins which block mevalonate synthase stimulate bone formation in animals].**
- **Thus, the mevalonate pathway appears to be important in bone cell function and provides new targets for drug development.**

Bisphosphonates

Adverse Effects:

1. **Gastric and esophageal irritation. Advise the patient to take the drug with a full glass of water and remain upright for 30 minutes.**
2. **High doses produce mineralization defect.**
3. **High doses cause renal deterioration and osteonecrosis of the jaw.**
4. **Over-suppression of bone turnover may cause subtrochanteric femur fractures in patients on long-term treatment.**

Bisphosphonates

Contraindications:

1. **Decreased renal function.**
2. **Esophageal motility disorders.**
3. **Peptic ulcer disease.**

Therapeutic uses:

1. **Hypercalcemia associated with malignancy.**
2. **Paget's disease.**
3. **Osteoporosis.**

Denosumab

- **Denosumab is a human monoclonal antibody that binds to and prevents the action of RANKL.**
- **RANKL is produced by osteoblasts and other cells, including T lymphocytes. It stimulates osteoclastogenesis via RANK, the receptor for RANKL that is present on osteoclasts and osteoclast precursors.**
- **By interfering with RANKL function, denosumab inhibits osteoclast formation and activity.**

Denosumab

- **It is at least as effective as the potent bisphosphonates in inhibiting bone resorption.**
- **Can be used in the treatment of:**

1. **Postmenopausal osteoporosis.**
2. **Some cancers (prostate and breast) to limit the development of bone metastases or bone loss resulting from the use of drugs that suppress gonadal function.**

Denosumab

- **Denosumab is administered subcutaneously every 6 months.**
- **The drug appears to be well tolerated but main concerns are:**

1. **Increased risk of infection because some immune cells express RANKL.**
2. **It can lead to transient hypocalcemia, especially in patients with marked bone loss or compromised calcium regulatory mechanisms, including chronic kidney disease and vitamin D deficiency.**

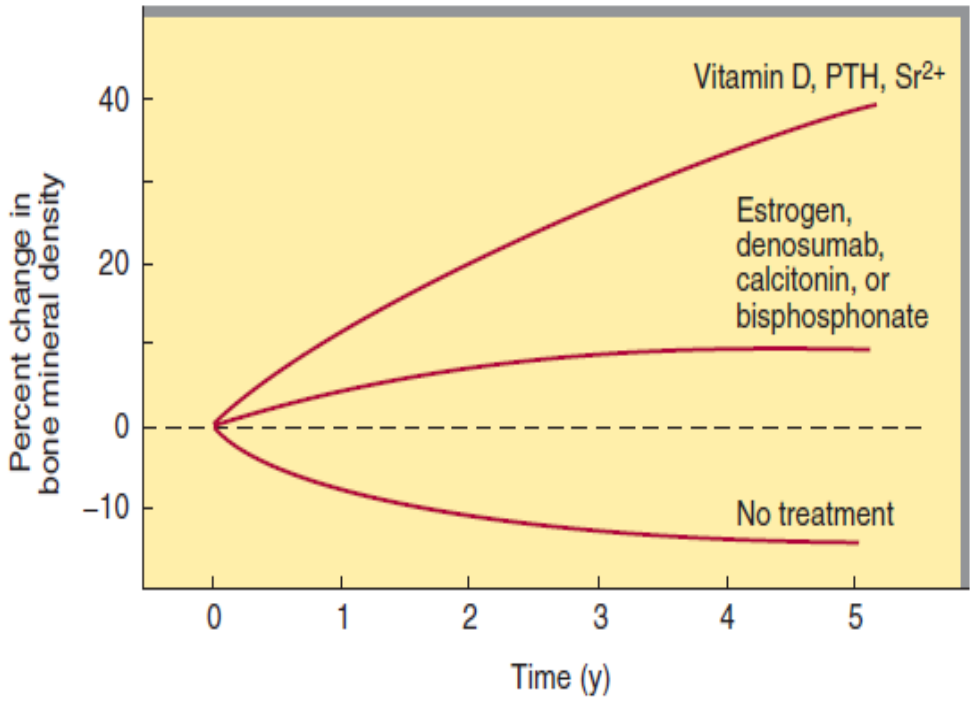


FIGURE 42–5 Typical changes in bone mineral density with time after the onset of menopause, with and without treatment. In the untreated condition, bone is lost during aging in both men and women. Strontium (Sr^{2+}), parathyroid hormone (PTH), and vitamin D promote bone formation and can increase bone mineral density in subjects who respond to them throughout the period of treatment, although PTH and vitamin D in high doses also activate bone resorption. In contrast, estrogen, calcitonin, denosumab, and bisphosphonates block bone resorption. This leads to a transient increase in bone mineral density because bone formation is not initially decreased. However, with time, both bone formation and bone resorption decrease with these pure antiresorptive agents, and bone mineral density reaches a new plateau.

Calcimimetics (Cinacalcet)

- Activates the calcium sensing receptor (CaSR) in the parathyroid gland, which blocks PTH secretion.
- Indicated for treatment of secondary hyperparathyroidism in chronic kidney disease and for treatment of parathyroid carcinoma.
- CaSR antagonists may be useful in hypoparathyroidism or to stimulate intermittent PTH secretion in the treatment of osteoporosis.

Plicamycin (Mithramycin)

- **Is a cytotoxic antibiotic.**
- **Binds to DNA and interrupts DNA directed RNA synthesis and thus protein synthesis.**
- **Indicated for treatment of Paget's disease and hypercalcemia (1/10 cytotoxic dose).**

Thiazide Diuretics

- **They reduce renal calcium excretion:**

1. **Enhance the effectiveness of PTH in stimulating reabsorption of calcium by the renal tubules.**
2. **In the distal tubule, thiazides block sodium reabsorption at the luminal surface, increasing the calcium-sodium exchange at the basolateral membrane and thus enhancing calcium reabsorption.**

Thiazide Diuretics

3. **Enhance calcium reabsorption secondary to increased sodium reabsorption in the proximal tubule.**

- **Indicated for hypercalciuria and stone formation in patients with idiopathic hypercalciuria. They decrease urine oxalate excretion and increase urine magnesium and zinc levels, both of which inhibit calcium oxalate stone formation.**

Strontium Ranelate

- **Strontium ranelate is composed of two atoms of strontium bound to an organic ion, ranelic acid.**
- **It is used in Europe for the treatment of osteoporosis.**
- **It blocks differentiation of osteoclasts while promoting their apoptosis, thus inhibiting bone resorption.**
- **It also promotes bone formation.**

Strontium Ranelate

- **Unlike bisphosphonates, denosumab, or teriparatide, this drug increases bone formation markers while inhibiting bone resorption markers.**
- **Large clinical trials have demonstrated its efficacy in increasing bone mineral density and decreasing fractures in the spine and hip.**