Corticosteroids

Multiple factors lead to corticosteroid-induced bone loss:

1. Decreased bone formation by increasing osteoblast apoptosis and decreasing growth factors involved in regenerating bone (osteoprogestins and insulin-like growth factor-1).
2. Increase bone resorption secondary to decreased levels of LH, FSH, testosterone, and estrogen).
3. induction of calcium deficiency by decreasing gastrointestinal absorption of calcium from the intestines and increasing its renal excretion.

Antiseizure Drugs

The medications most commonly associated with osteoporosis include phenytoin, phenobarbital, carbamazepine, and primidone. All are inducers of CYP-450 isoenzymes.

1. Induction hepatic CYP-450 enzymes, leading to rapid metabolism of vitamin D, and possibly, estrogen.
2. Decreased fractional calcium absorption, secondary hyperparathyroidism
3. Increased bone turnover.

- phenytoin and carbamazepine have exhibited direct effects on the bone by inhibiting osteoblast cells.
- phenytoin inhibits osteocalcin secretion (a hormone that regulates calcium in the bone).

Heparin

With long-term, high-dose therapy (≥ six months).

The exact cellular mechanism in which heparin induces bone loss is not completely understood.

1. It causes increased bone resorption by stimulating osteoclasts and suppressing osteoblast function, leading to decreased bone mass.
2. Other mechanisms may be depletion of mast cells in bone marrow and enhancement of parathyroid hormone (PTH) function.
3. PTH increases the release of calcium and phosphorus from bone into the blood to elevate serum levels
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Progestins

The progestin preparation most often associated with bone loss is medroxyprogesterone acetate (MPA). The risk of bone loss increases after two years of continuous use of MPA.

1. It suppresses ovarian production of estrogen. Estrogen is protective against bone loss, and as previously noted, low levels of estrogen can lead to deterioration of bone mass.
2. It also inhibits gonadotropins secretion (LH and FSH).
3. It exhibits corticosteroidal properties and can decrease osteoblast differentiation by occupying the glucocorticoid receptor.

Thiazolidendiones:

They simultaneously inhibit osteoblast differentiation and activate osteoclast differentiation, leading to bone loss due to decreased bone formation and increased bone resorption.

Methotrexate:

It may raise the risk of osteoporosis when used in very high doses, such as in oncology patients. The mechanism is not completely understood but is thought to involve an imbalance of bone resorption and formation.

Loop diuretics (furosemide):

May decrease bone mass by increasing calcium excretion by the kidneys.

Excess thyroid supplementation:

This usually occurs only when the thyroid-stimulating hormone level is virtually undetectable due to oversupplementation.

The effect is demineralization of the bone.

Aluminum-containing antacids:

Can bind calcium in the gastrointestinal tract and lead to decreased calcium absorption.

Lithium:

Has been shown to increase PTH secretion which can cause calcium release from the bone.

Warfarin:

There is a controversial argument for warfarin and loss of vitamin K causing impaired bone formation.

Long-term warfarin therapy may be associated with bone mineral loss and vascular calcification in 60–80 year old hypertensive patients.

There are three typical Vitamin K dependent proteins: osteocalcin (OC), matrix Gla protein (MGP), and growth arrest specific protein 6 (Gas-6) which play key functions in maintaining bone strength, vascular calcification inhibition, and cell growth regulation, respectively. On the other hand, warfarin prevents the activation of MGP and Gas-6; therefore, long-term use of warfarin is reported to be associated with osteoporotic fractures. In addition, it is known that low vitamin K is associated with reduced bone mineral density

Canagliflozin:

SGLT2 inhibitors may have potential adverse effects on bone, including increased fracture risk and decreased bone mineral density (BMD).

Across clinical studies, canagliflozin was not associated with meaningful changes in serum or urine calcium, vitamin D, or parathyroid hormone. Canagliflozin was

associated with increases in serum collagen type 1 beta-carboxy telopeptide (beta-CTX), a bone resorption marker, and osteocalcin, a bone formation marker. Decreases in total hip BMD were seen with canagliflozin. The reason for increased fracture risk with canagliflozin treatment is unknown, but is likely not related to a direct effect of canagliflozin on bone-related biomarkers.

Mast cells:

The mast cell stores a number of factors known to affect bone metabolism. Patients with systemic mastocytosis often demonstrate osteoporosis and bone marrow mast cells may be increased in osteoporotic postmenopausal women and in men. Their deficiency has been associated with low remodeling states, while their excess is associated with accelerated bone loss.

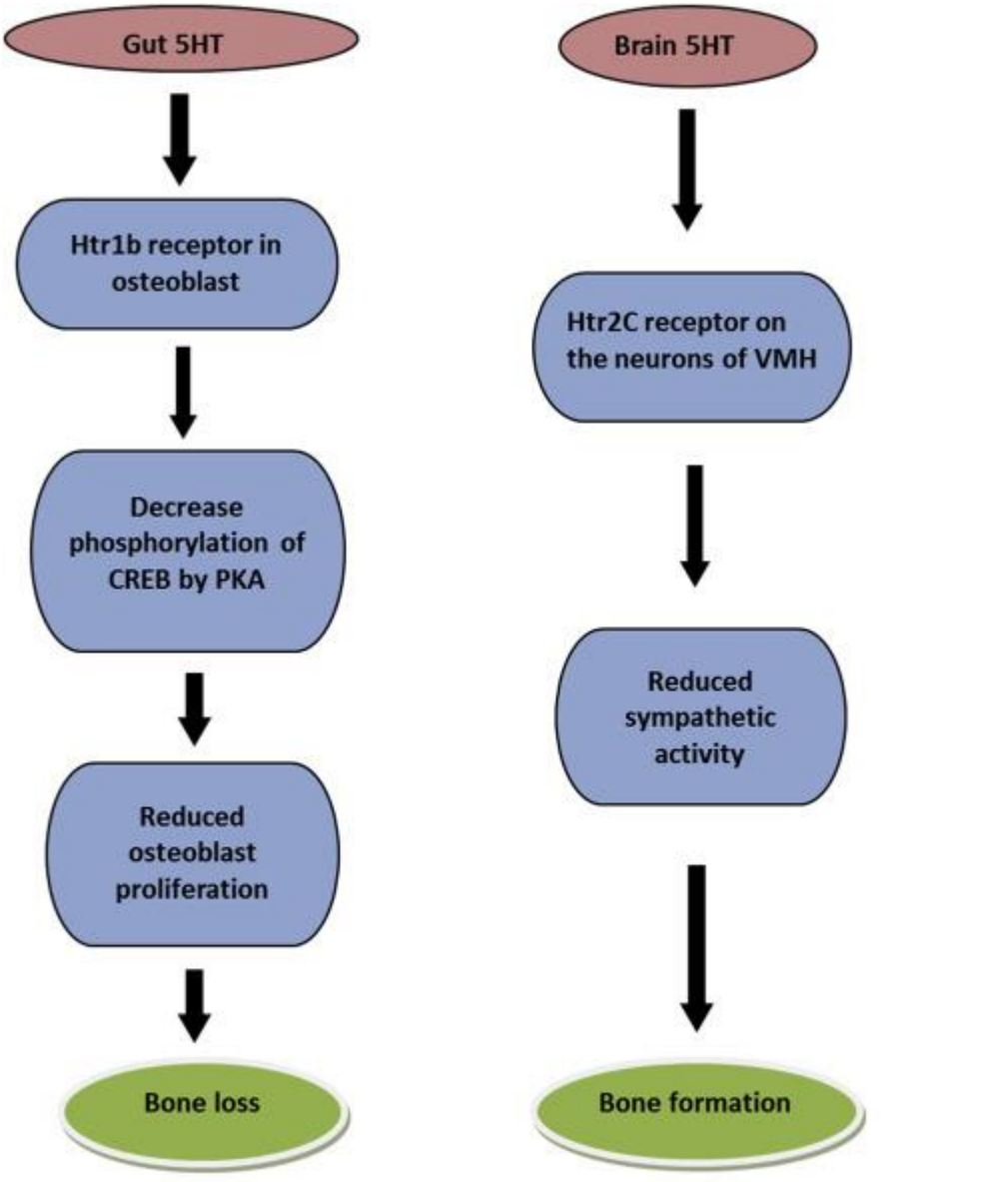
Selective Serotonin Reuptake Inhibitors (SSRIs):

The use of antidepressants at therapeutic doses is associated with decreased bone mineral density and increased fracture risk.

SSRIs are more concentrated in the bone marrow as compared to the brain or blood.

Gut derived serotonin reduces the osteoblast proliferation and thus leads to bone loss, while brain derived serotonin decreases sympathetic output and thus favors bone formation.

Brain derived serotonin reduces the epinephrine / sympathetic tone and this reduced sympathetic outflow. β_2-adrenergic receptors on the osteoblast enhances the bone formation and reduces bone resorption.



Oury et al., 2010 [37] Ducy and Karsenty, 2010 [36]