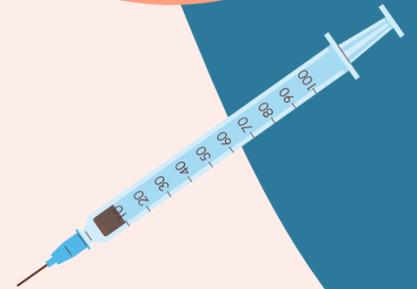




ENDOCRINE PHARMACOLOGY REVISION

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Anti-Hyperglycemic agents

Other Antidiabetic drugs

Insulin

Release insulin (Insulin secretagogues)

Other mechanism

Sulfonylureas

Meglitinides

Insulin sensitizers

↓ intestinal glucose absorption

Incretin-based therapy

↑ urinary glucose excretion

**Biguanides
Metformine**

**Thiazolidinediones
(pioglitazone)**

**α-glucosidase inhibitors
(acarbose)**

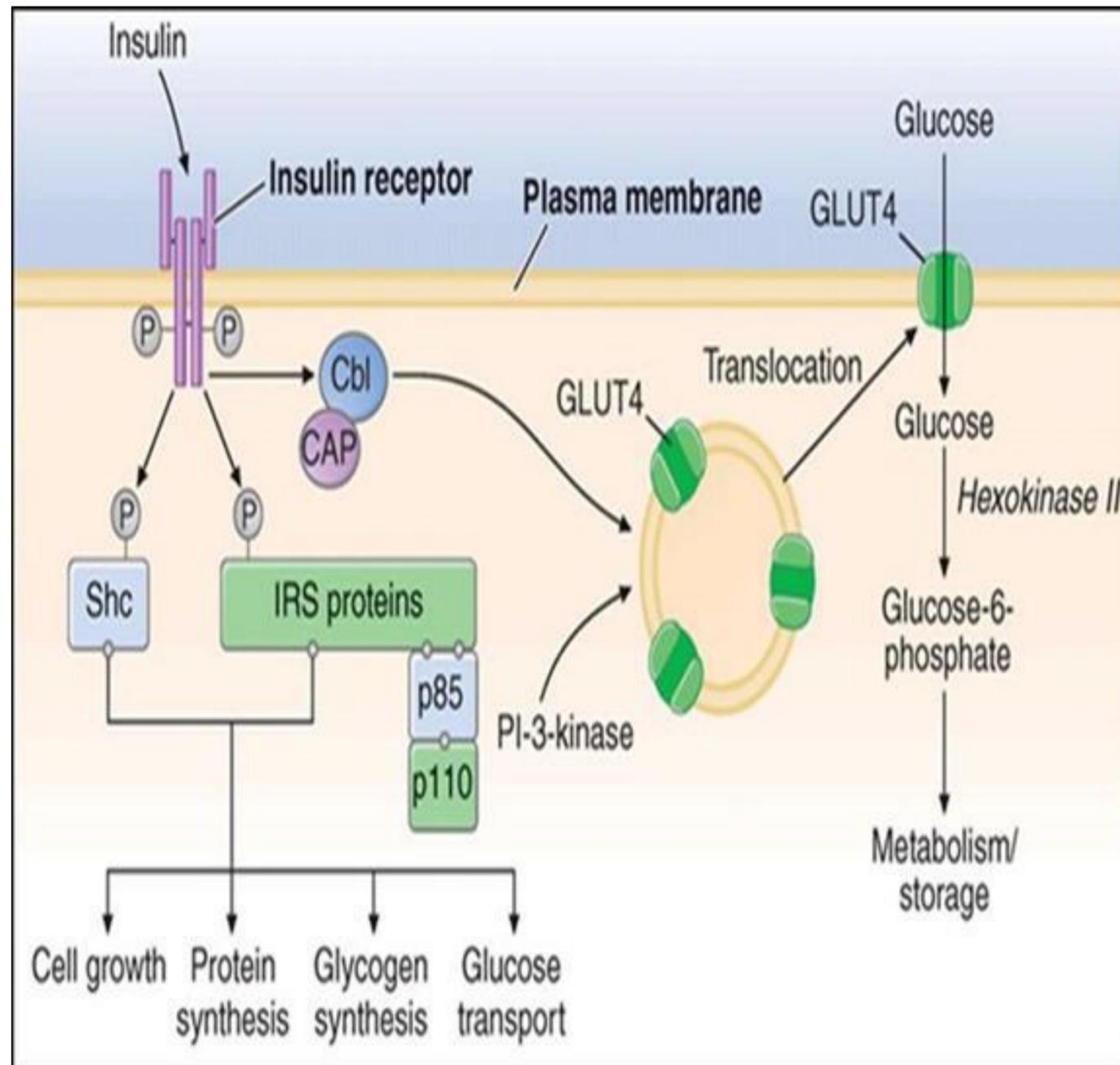
**GLP-1 analog
(exenatide)**

**DPP-4 inhibitor
(sitagliptin)**

**SGLT2 inhibitors
(canagliflozin)**

Mechanism of action of Insulin

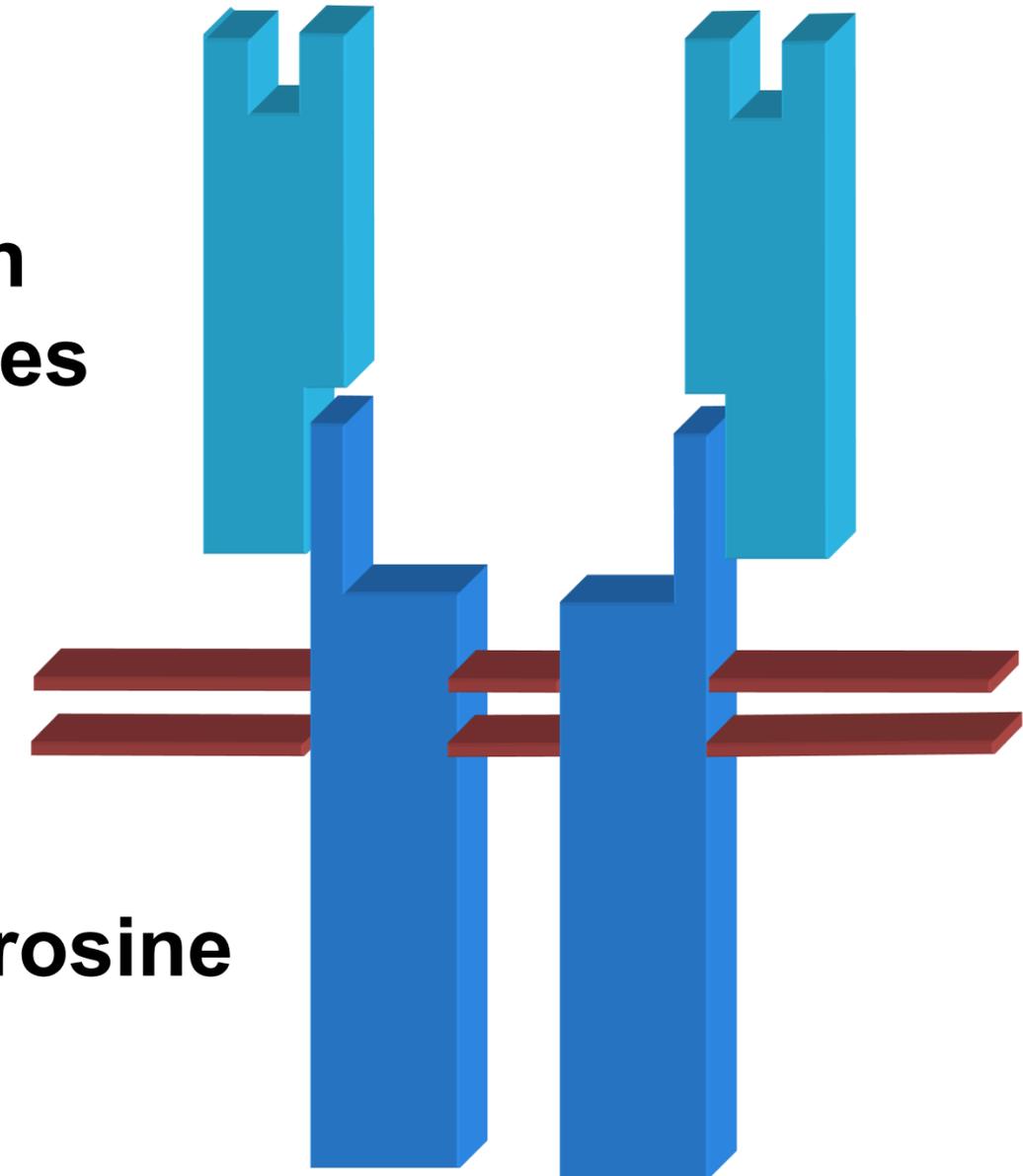
Cell-surface receptors:



α subunits contain insulin binding sites

plasma membrane

β subunits have tyrosine kinase activity



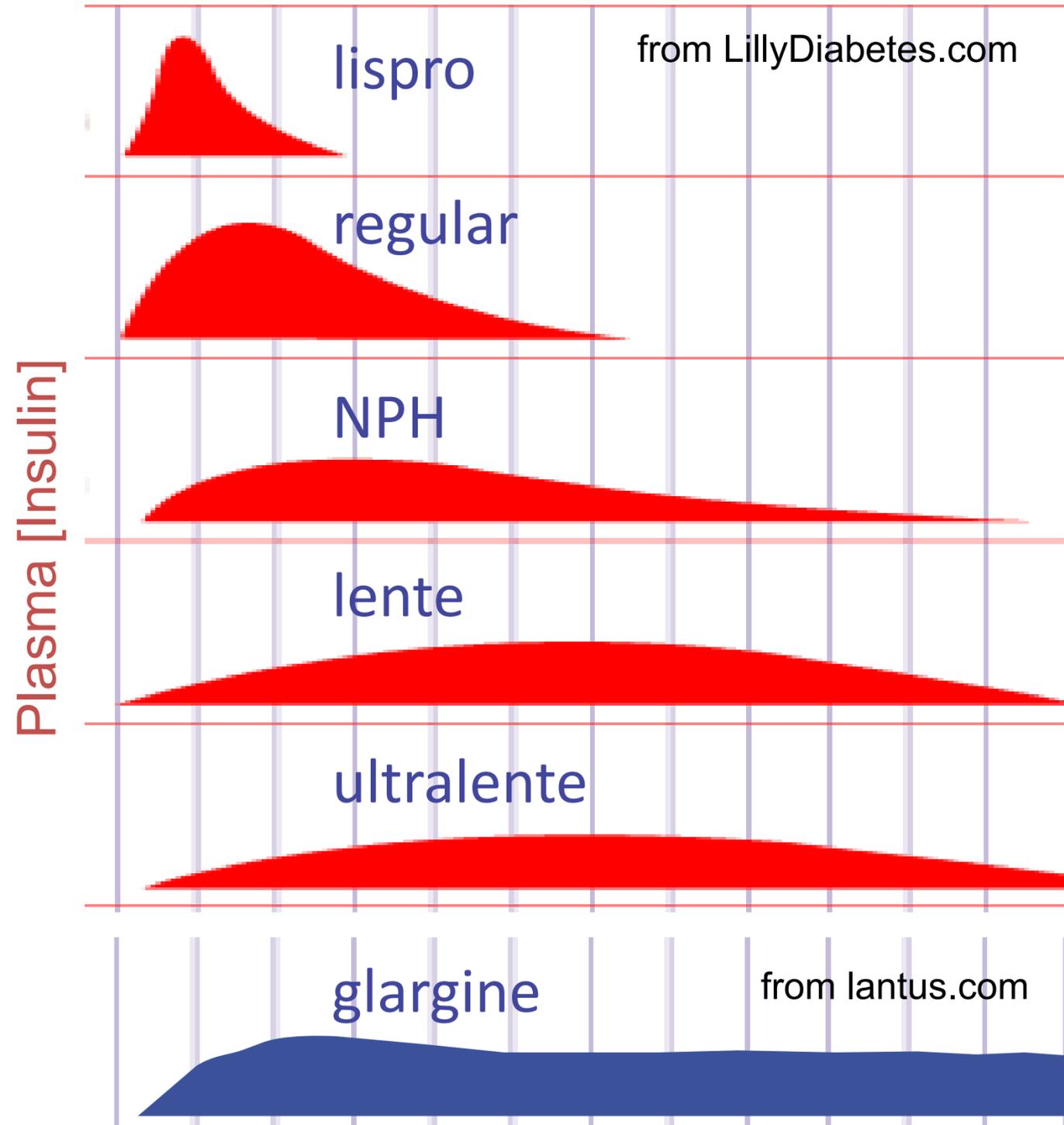
Insulin Preparations

Rapid-acting

Short-acting

Intermediate-acting

Long-acting



Clinical Indications of Insulin

- 1. Type 1 diabetes mellitus: absolutely in all cases**
- 2. Type 2 diabetes mellitus: if:**
 - After failure of oral drugs.**
 - Stress conditions” e.g. infections, surgery, or pregnancy.**
- 3. Diabetic ketoacidosis (DKA): regular insulin is the only type used i.v.**
- 4. Treatment of acute hyperkalemia**

Adverse Effects of Insulin Therapy

1. Hypoglycemia: the most common and dangerous side effect.

➤ Treatment:

If the patient is conscious or semiconscious → give him sugar solution.

If the patient is in deep coma:

✓ i.v. glucose

✓ i.m. Glucagon

2. Hypersensitivity reactions (rare).

3. General weight gain

4. Insulin resistance

5. Hypokalemia

6. Local adverse effects:

▪ Allergy: at the site of injection ttt by Change the type of insulin & Local corticosteroids.

▪ Lipodystrophy: (atrophy or hypertrophy) ttt by rotating the injection site.

▪ Local infection.

Drugs	Mechanism of Action	Adverse effects
Sulphonylureas e.g, Glipizide	Increases insulin secretion from pancreatic beta cells by closing ATP-sensitive K ⁺ channels, leading to depolarization, increased Ca ²⁺ entry via voltage-dependent calcium channels	<ol style="list-style-type: none"> 1. Hypoglycemia 2. weight gain
Meglitinides e.g, Repaglinide, nateglinide	Increases insulin secretion from pancreatic beta cells by closing ATP-sensitive K ⁺ channels, leading to depolarization, increased Ca ²⁺ entry via voltage-dependent calcium channels	<ol style="list-style-type: none"> 1. Less hypoglycemia 2. Less weight gain 3. They don't contain sulfur, so they can be used in patients allergic to sulphonylureas.
Biguanides Metformin	<ol style="list-style-type: none"> 1- in the liver → inhibition of gluconeogenesis 2- ↑ Insulin sensitivity & ↑ glucose uptake in skeletal muscle and adipose tissue 3- ↓ Glucose absorption from the intestines 	<ol style="list-style-type: none"> 1. *Gastrointestinal disturbances 2. *Lactic acidosis so CI in patient with renal or hepatic disease, or alcoholics 3. *Vitamin B12 deficiency

Drugs	Mechanism of Action	Adverse effects
<p>Thiazolidinediones e.g., Pioglitazone</p>	<p>Regulates gene expression by binding to PPAR-γ that regulates cellular glucose transporters</p> <p>\uparrow Number of GLUT4 glucose transporters in cell membranes of muscle and adipose tissue \rightarrow \uparrow peripheral uptake of glucose</p>	<p>1-Cardiovascular SEs \rightarrow \uparrow plasma volume, edema and \uparrow risk of developing heart failure</p> <p>2- Increased body weight</p> <p>3-slight \uparrowRisk of bladder cancer</p> <p>4-Osteoporosis & fractures</p>
<p>Glucagon-Like Peptide 1 Agonists e.g., Exenatide</p>	<p>Analog of glucagon-like peptide-1 (GLP-1) activates GLP-1 receptors</p> <p>It is a synthetic GLP-1 analog that \uparrow insulin secretion and \downarrow glucagon secretion.</p> <p>It slows gastric emptying and \downarrow appetite.</p>	<p>1. GI disturbances, headache,</p> <p>2. pancreatitis</p>
<p>Dipeptidylpeptidase-4 inhibitors e.g., Sitagliptin</p>	<p>Inhibitor of the dipeptidyl peptidase-4 (DPP-4) that degrades GLP-1 and other incretins</p>	<p>1. GI upset, headache.</p> <p>2. Small risk of acute pancreatitis</p>

Drugs	Mechanism of Action	Adverse effects
<p>α-glucosidase inhibitors (Acarbose)</p>	<p>Inhibit intestinal α-glucosidase and reduce absorption of carbohydrates</p>	<p>1-Flatulence and abdominal bloating → most common</p> <p>2-↓ iron absorption.</p>
<p>SGLT2 inhibitors (Canagliflozin, Dapagliflozin)</p>	<p>Via inhibiting SGLT-2, it inhibits reabsorption of glucose filtered at the proximal tubules. This leads to glucosuria and lowered blood glucose in type 2DM, as well as weight loss.</p>	<p>1. Osmotic diuresis and increase the risk of hypovolemia</p> <p>2. Genital and urinary tract infections</p>

which of the following drugs cause this hypoglycemia?

A. Metformine.

B. Pioglitazone.

C. Sitagliptin.

D. Acarbose.

E. Glipizide



Which of the following molecular actions most likely mediated the therapeutic effect of Sitagliptin?

- A.** Inhibition of dipeptidyl peptidase-4
- B.** Inhibition of α -glycosidase
- C.** Activation of AMP-activated protein kinase
- D.** Activation of glucagon-like peptide (GLP)-1 receptors
- E.** Blockade of ATP-sensitive K⁺ channels



A 54-year-old patient was started on a new antidiabetic medication 10 days ago. Physical examination showed peripheral edema, mild jugular venous distension. **Which of the following drugs is most likely to have caused his new symptoms?**

A. Acarbose

B. Pioglitazone

C. Metformin

D. Dapagliflozin

E. Glyburide



The PPAR- γ receptor that is activated by thiazolidinediones increases tissue sensitivity to insulin by which of the following mechanisms?

- (A)** Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
- (B)** Inactivating a cellular inhibitor of the GLUT2 glucose transporter
- (C)** Inhibiting acid glucosidase, a key enzyme in glycogen breakdown pathways
- (D)** Regulating transcription of genes involved in glucose utilization
- (E)** Stimulating the activity of a tyrosine



Which of the following actions most likely mediated the antidiabetic effect of Metformin?

- A.** Decreased breakdown of glycogen
- B.** Decreased intestinal glucose absorption
- C.** Increased insulin secretion from pancreas
- D.** Increased glucose excretion in urine
- E.** Decreased glucose output from the liver



Which of the following agents should be administered to achieve rapid control of the severe ketoacidosis?

(A) Crystalline zinc insulin

(B) Glyburide

(C) Insulin glargine

(D) NPH insulin

(E) Tolbutamide



Which of the following is an important effect of insulin?

- (A)** Increased conversion of amino acids into glucose
- (B)** Increased gluconeogenesis
- (C)** Increased glucose transport into cells
- (D)** Inhibition of lipoprotein lipase
- (E)** Stimulation of glycogenolysis



A 54-year-old obese patient with type 2 diabetes has a history of alcoholism. In this patient, metformin should either be avoided or used with extreme caution because the combination of metformin and ethanol increases the risk of which of the following?

- (A)** A disulfiram-like reaction
- (B)** Excessive weight gain
- (C)** Hypoglycemia
- (D)** Lactic acidosis
- (E)** Serious hepatotoxicity



Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?

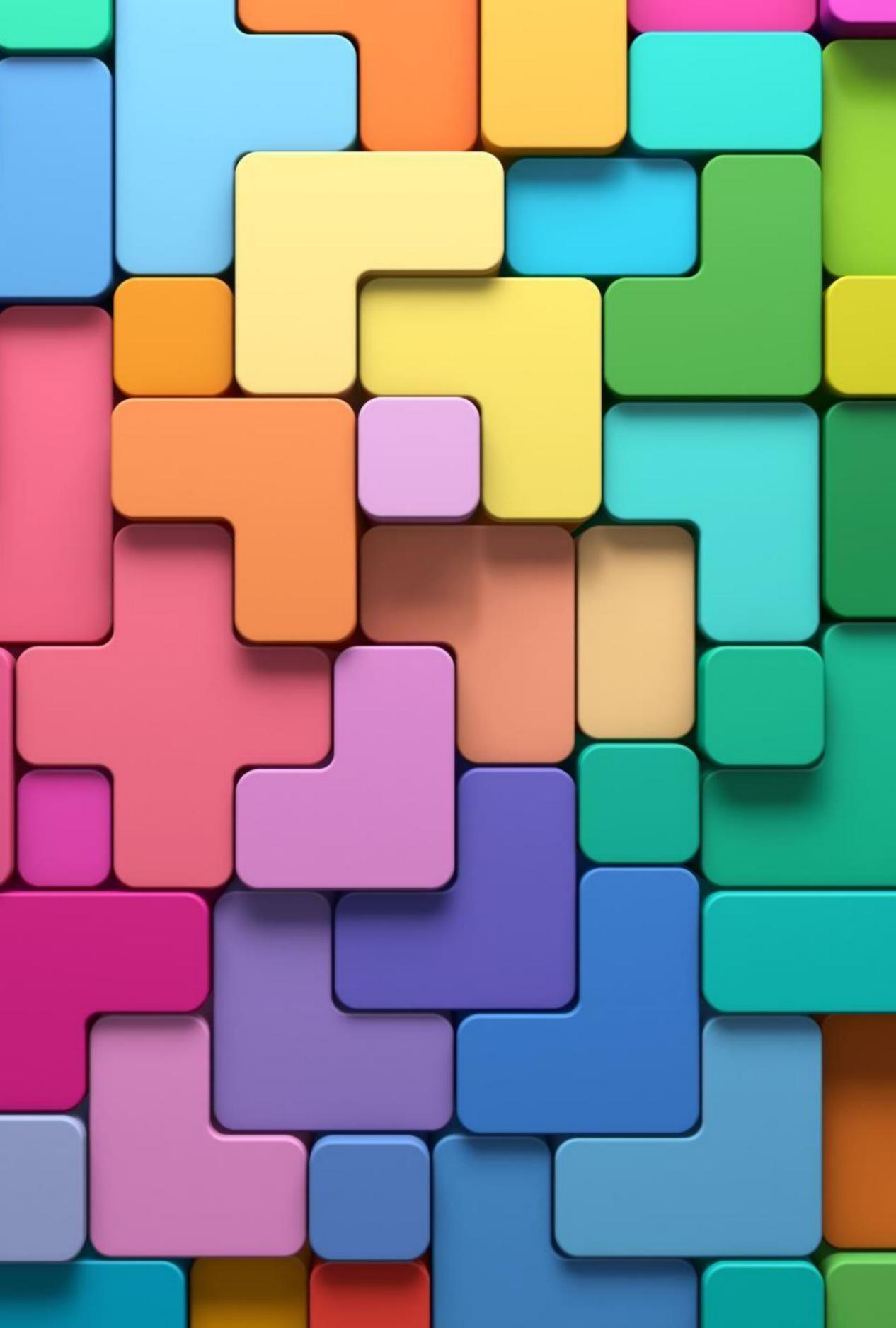
- (A)** Acarbose
- (B)** Exenatide
- (C)** Glipizide
- (D)** Pioglitazone
- (E)** Repaglinide



Which of the following is the most likely complication of insulin therapy ?

- (A)** Dilutional hyponatremia
- (B)** Hypoglycemia
- (C)** Increased bleeding tendency
- (D)** Pancreatitis
- (E)** Severe hypertension





Thyroid disorders

Pharmacology

How should hyperthyroidism be treated?

The three main treatment options are

➤ **Antithyroid drugs** include:

1. **Thioamide drugs** → ↓ synthesis of thyroid hormones as methimazole (MMI) and propylthiouracil (PTU).

(MMI is almost always the preferred agent. Because of concerns about severe hepatotoxicity, PTU is recommended only in

(1) the first trimester of pregnancy

(2) thyroid storm therapy, because of the ability of PTU to block T4-to-T3 conversion)

2. **Iodide salts** → ↓ release of thyroid hormones

3. **Beta (β)-blockers** → ↓ symptoms of sympathetic overactivity → control CVS symptoms of hyperthyroidism

➤ **Radioiodine (I¹³¹) ablation**

➤ **Surgery (thyroidectomy)**

Thioamides

Methimazole & propylthiouracil (PTU)

Preferred line of therapy

← Methimazole →

MOA

- Block T4 & T3 synthesis

Efficacy

- More effective

t1/2

- Longer → 8 h → once daily

Plasma protein binding

Not bound → crosses placenta and appears in breast milk →

Use in pregnancy

- x3 more likely to cause birth defects (esp. during 1st trimester of pregnancy)

Liver toxicity

- Lower risk

Leukopenia

- Lower risk



PTU →

- Same + *inhibits the peripheral conversion of T4 to T3.*

- Less effective

- Short → 2 h → 2-3 times/day

- 80% bound

- Drug of choice just before and during 1st trimester of pregnancy.

- Higher risk

- Higher risk

β -adrenergic receptor blockers

MOA of β -blockers in hyperthyroidism →

- β -blockers → propranolol & atenolol → used to ↓ CVS symptoms associated with hyperthyroidism
- Propranolol, but **NOT** other beta blockers → ↓ peripheral conversion of T4 to T3
- If beta blockers are CI → Calcium channel blockers can be used → diltiazem

Radioactive iodine (I 131).. (RAI)

SE →

- 80% to 90% of ptns become hypothyroid → require lifelong thyroid hormone replacement.

CI→

- Pregnant women → but it is NOT teratogenic if pregnancy occurs after I¹³¹ therapy.
- Young children
- Ptns with thyroid cancer
- Ptns with moderate to severe Graves-related eye disease
- Ptns with heart disease (unless controlled)

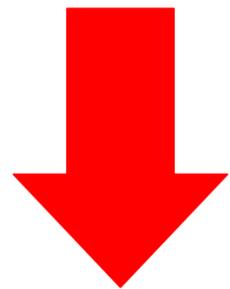
Table 44.4 Treatments available for thyrotoxicosis

	Adverse effects (%)	Contraindications	Cautions
Thionamides Carbimazole Propylthiouracil	Rash/arthropathy (5%) Agranulocytosis (0.3%) Hepatitis (rare)	Previous severe allergy Cross-reactivity in 10%	Pregnancy: propylthiouracil is preferred Do not use block/replace regimens
Radioiodine	Hypothyroidism requiring lifelong T ₄	Pregnancy	Ensure euthyroid first Ophthalmopathy may deteriorate
Surgery	Hospital stay Neck scar Surgical/anaesthetic risk 10–75% requires T ₄		Ensure euthyroid first Ophthalmopathy may deteriorate

T₄, thyroxine.

How should hypothyroidism be treated?

- All patients with overt hypothyroidism should be treated with **levothyroxine** replacement therapy (LT4).
- Treatment is also generally recommended for subclinical hypothyroidism.
- Regular monitoring and dose adjustment is recommended.



Levothyroxine → often start with lower dose, esp. in old ptns & those with long-standing/severe hypothyroidism → then gradually increase dose → to prevent excessive stress on the CVS



A 53-year-old woman with the diagnosis of Graves disease is being treated with radioactive iodine. She should be warned of the high likelihood of

- a. hyperthyroidism.
- b. iodism.
- c. hypothyroidism
- d. thyroid nodules.
- e. thyroid cancer



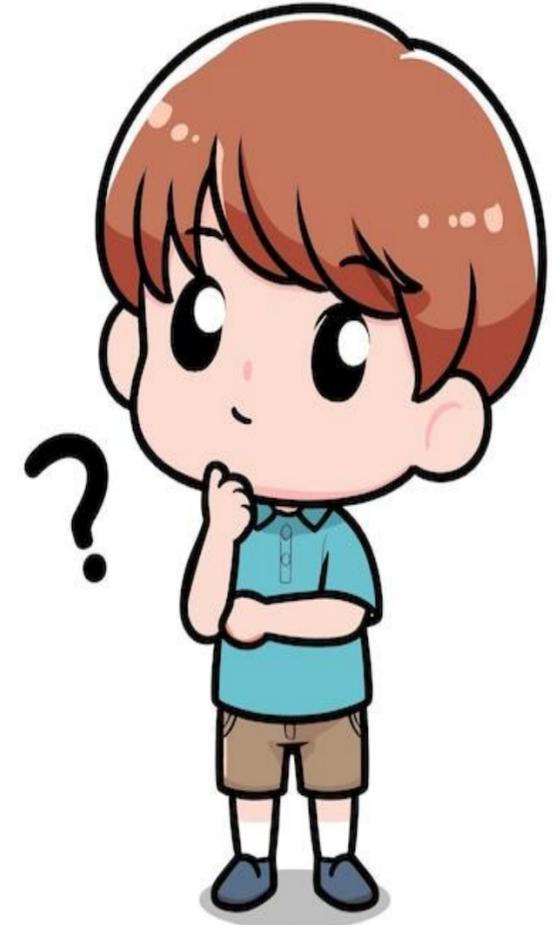
Methimazole reduces serum concentration of T₃ primarily by which of the following mechanisms?

- (A) Accelerating the peripheral metabolism of T₃
- (B) Inhibiting the proteolysis of thyroid-binding globulin
- (C) Inhibiting the secretion of TSH
- (D) Inhibiting the uptake of iodide by cells in the thyroid
- (E) Preventing the addition of iodine to tyrosine residues on thyroglobulin



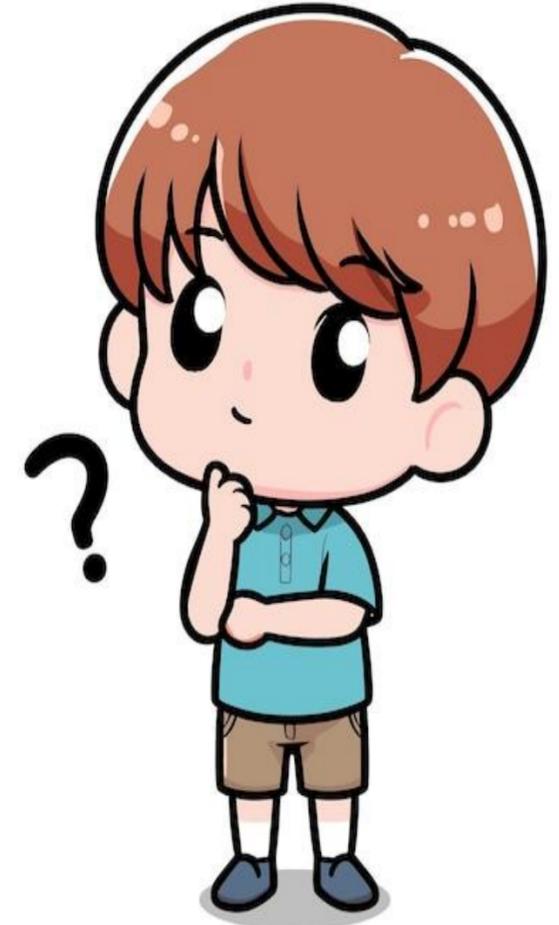
Though rare, a serious toxicity associated with the thioamides is which of the following?

- (A)** Agranulocytosis
- (B)** Lupus erythematosus-like syndrome
- (C)** Myopathy
- (D)** Torsades de pointes arrhythmia
- (E)** Thrombotic thrombocytoc purpura (TTP)



Which of the following is a sign or symptom that would be expected to occur in the event of chronic overdose with exogenous T₄?

- (A)** Bradycardia
- (B)** Dry, puffy skin
- (C)** Large tongue and drooping of the eyelids
- (D)** Lethargy, sleepiness
- (E)** Weight loss



A 65-year-old man with multinodular goiter is scheduled for a near-total thyroidectomy. Which of the following drugs will be administered for 10–14 d before surgery to reduce the vascularity of his thyroid gland?

- (A) Levothyroxine**
- (B) Liothyronine**
- (C) Lugol's solution**
- (D) Prednisone**
- (E) Radioactive iodine**



When initiating T4 therapy for an elderly patient with long standing hypothyroidism, it is important to begin with small doses to avoid which of the following?

- (A)** A flare-up of exophthalmos
- (B)** Acute renal failure
- (C)** Hemolysis
- (D)** Overstimulation of the heart
- (E)** Seizures

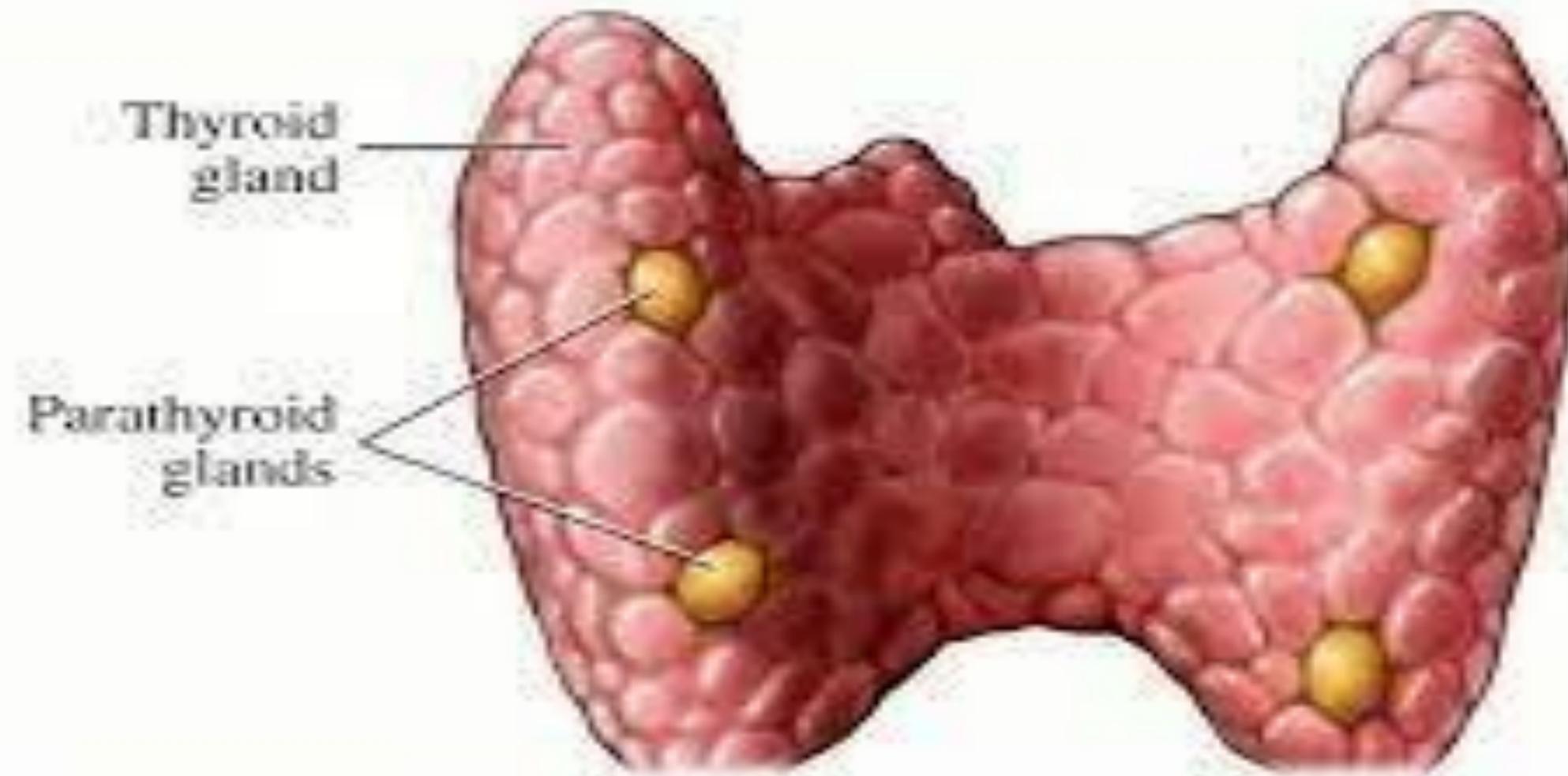


A 48-year-old woman with Graves disease with severe hyperthyroidism is being treated with radioactive iodine. She is also being treated with methimazole because of

- a. the long period of time before hyperthyroidism is controlled by radioactive iodine.
- b. the expectation that radioactive iodine will be ineffective.
- c. methimazole is better absorbed than radioactive iodine.
- d. methimazole will counteract the side effects of radioactive iodine.
- e. radioactive iodine is not active unless administered with methimazole



Drugs affecting ca homeostasis & ttt of osteoporosis



Regulators of Ca²⁺ metabolism

Hormonal

Primary

Parathormone

Vitamin D

Calcitonin

secondary

Glucocorticoids

Estrogen

Raloxifene

Non- hormonal

Bisphosphonates

Densumab

Cinacalcet

Thiazides

Na fluoride

Drugs	Mechanism of Action	Uses
Parathormone (PTH)	Acts on specific receptors on bone and kidney \uparrow serum Ca and \downarrow serum PO4	<p>1-PTH (84 amino acids) In hypoparathyroidism as an adjunct to Ca and vit D</p> <p>2-Teriparatide (34 amino acids) in treatment of osteoporosis.</p>
Vitamin D	Acts on DNA receptors to synthesis protein for Ca transport: <ul style="list-style-type: none"> ▪ Bone: when bone Ca is deficient (rickets) Vit D increase Ca deposition. ▪ Intestine: increase calcium absorption. ▪ Kidney: increase reabsorption of Ca and PO4. 	<p>1-Treatment of hypocalcemia</p> <p>2-Treatment of osteoporosis.</p> <p>3-Treatment of rickets (children) and osteomalacia (adults).</p>
Calcitonin	Acts on specific receptors on bone and kidney \downarrow serum Ca and PO4	<p>1-Hypercalcemia and hyperphosphatemia</p> <p>2-Osteoporosis</p>

Drugs	Mechanism of Action	Uses
Glucocorticoids	<ul style="list-style-type: none"> ▪ ↑ Renal Ca²⁺ excretion ▪ Antagonize intestinal Vit D stimulated Ca absorption ▪ ↓ Bone formation (inhibit the osteoblast). 	<p>treat hypercalcemia</p> <p>associated with lymphoma</p>
Estrogen	<p>Estrogen receptors is present in bone (↓ bone resorption)</p>	<p>treatment of postmenopausal osteoporosis</p>
Raloxifene	<ul style="list-style-type: none"> -Mixed agonist-antagonist. - Stimulate estrogen receptors in bones and block them in the breast and uterus 	<p>treatment of postmenopausal osteoporosis</p>

Drugs	Mechanism of Action	Uses
<p>Bisphosphonates (Alendronate)</p>	<p>They inhibit many osteoclastic cell and induces apoptosis of the osteoclasts.</p>	<p>1-Treatment of osteoporosis 2-Treatment of hypercalcemia associated with malignancy</p> <p>AEs:</p> <p>1-Gastrointestinal distress. 2-High doses can cause renal impairment and osteonecrosis of the jaw.</p>
<p>Densumab</p>	<ul style="list-style-type: none"> ▪ Monoclonal antibody binds to RANKL with high affinity and blocks it from binding to its receptor RANK, thus inhibiting osteoclast maturation and bone resorption. 	<p>1-Skeletal-related events secondary to multiple myeloma or bone metastases. 2-Hypercalcemia of malignancy (don't response well to bisphosphonate) 3-Osteoporosis</p>

Drugs	Mechanism of Action	Uses
Cinacalcet	<ul style="list-style-type: none"> ▪ an agonist at the calcium-sensing receptor in the parathyroid gland increasing the activation of these calcium-sensing receptors to extracellular calcium. ▪ leads to decreased secretion of PTH and lowering of serum calcium levels. 	<p>1-Treatment of hyperparathyroidism.</p> <p>2-Treatment of hypercalcemia in patients with parathyroid cancer.</p>
Thiazides	<ul style="list-style-type: none"> ▪ decrease renal Ca²⁺ excretion through ↑ the effect of PTH in stimulating renal Ca²⁺ reabsorption 	
Sodium Fluoride	<p>Fluoride replaces the hydroxyl group in calcium phosphate salts (hydroxyapatite) to form fluorapatite.</p> <p>Fluorapatite deposited on the tooth surface is more resistant to erosion than hydroxyapatite.</p>	<p>1-Prevention of dental caries.</p> <p>2-Treatment of osteoporosis</p>

Treatment of osteoporosis

Prevention and treatment of osteoporosis

1 Replacement therapy

- Diet rich in calcium
- Vitamin D

2-Antiresorptive drugs

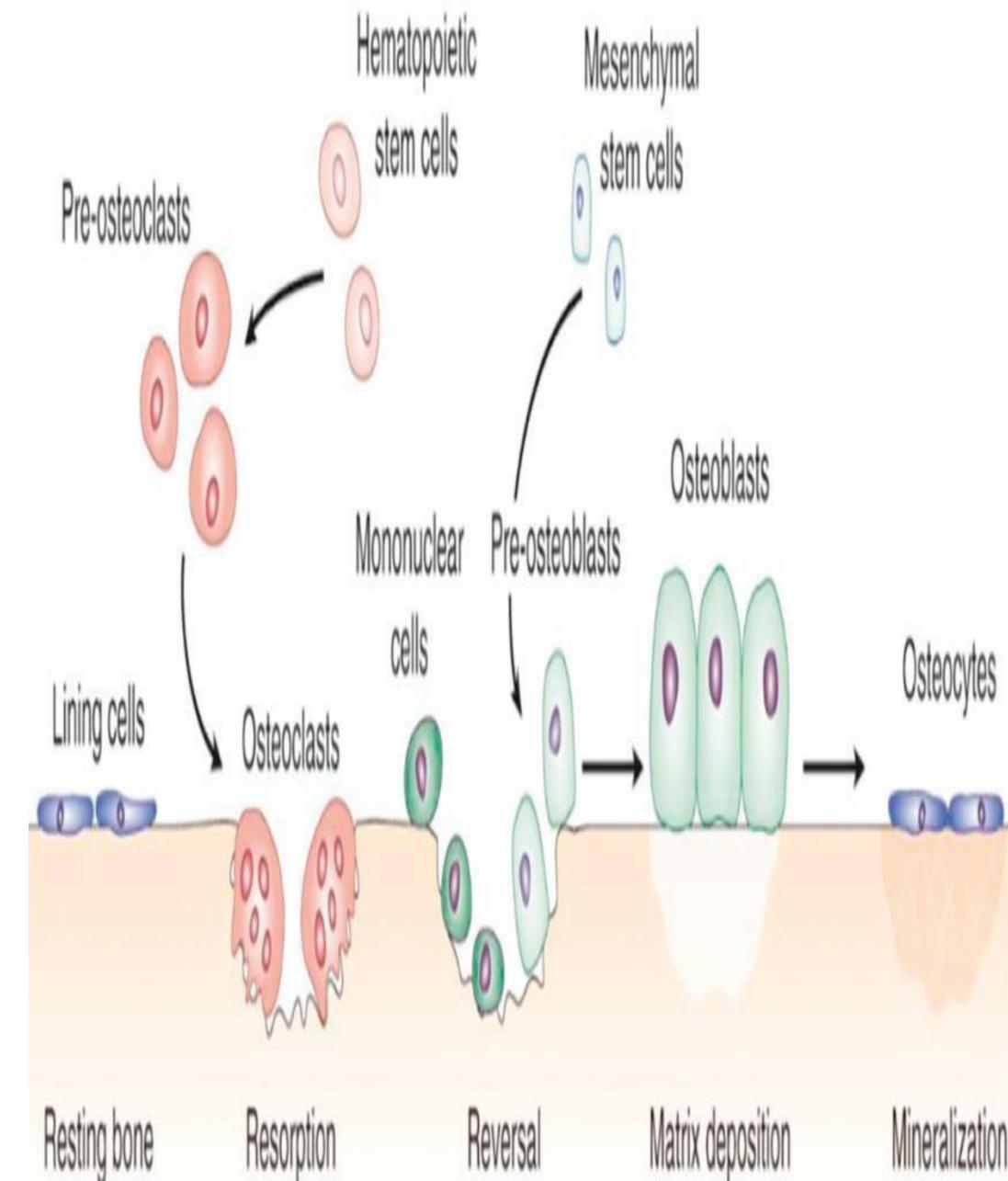
- Bisphosphonates (the first line)
- Selective Estrogen Receptor Modulators (Raloxifen)
- Calcitonin
- Denosumab

3- Anabolic drug

- Teriparatide

4-Anabolic antiresorptive

- Strontium ranelate



Osteonecrosis of the jaw is an adverse effect of which of the following drugs?

A. Estrogen.

B. Corticosteroid.

C. Bisphosphonates.

D. Calcitonin

E. Teriparatide



Which one of the following drugs can be used in treatment of hypercalcemia?

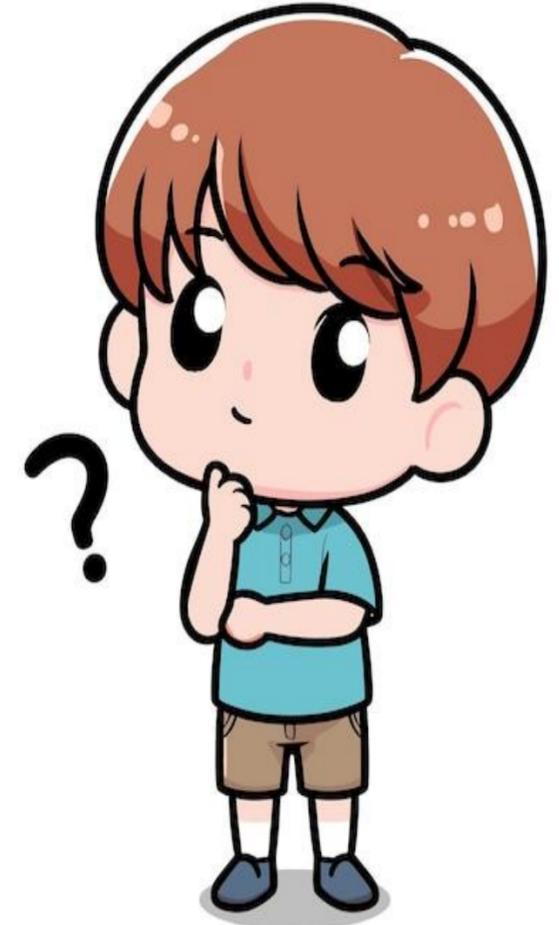
A: Thiazide diuretics

B: Vitamin D

C: Calcitonin

D: Parathyroid hormone

E: Teriparatide



which one of the following drugs could be used to treat hypercalcemia associated with bone metastasis?

A: Bisphosphonate

B: Thiazide diuretics

C: Vitamin D

D: Parathyroid hormone

E: Teriparatide



The following is recombinant PTH which is anabolic agent used in treatment of osteoporosis?

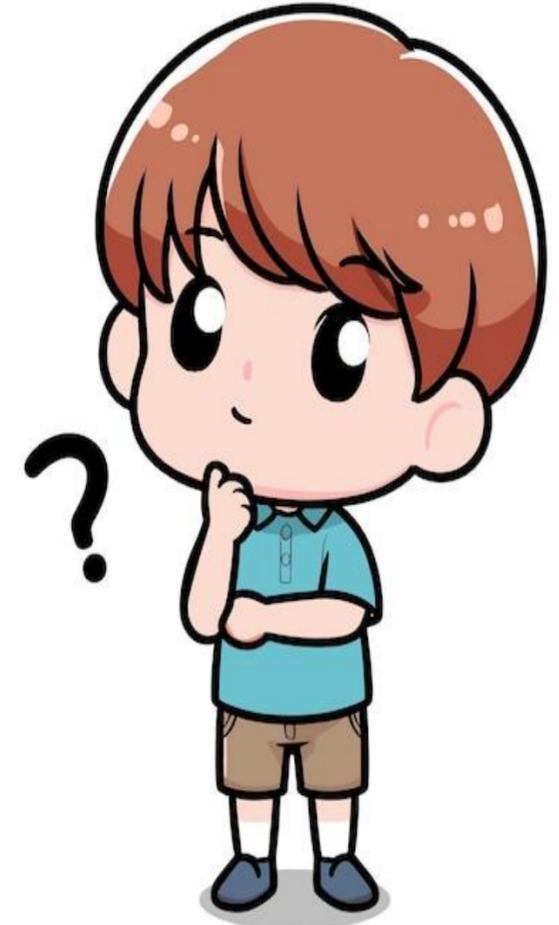
a) Estrogen

b) Bisphosphonates

c) Raloxifene

d) Prednisolone

e) Teriparatide





Thank
you