**Hypothalamic & Pituitary Hormones**

**1) Growth Hormone (Somatotropin)**

- Recombinant human GH (rhGH) is available for clinical use (Somatropin).

- Effects are mediated through **binding to a cell surface receptor of the JAK/STAT cytokine receptor superfamily**.

- **The growth promoting effect** is mediated mainly through **production of insulin-like growth factor 1 (IGF-1).**

- **GH** stimulates longitudinal bone growth

- **GH** has anabolic effects in muscles and catabolic effects in adipose tissue

- **GH** reduces insulin sensitivity resulting in mild **hyperinsulinemia**, and increased blood glucose levels.

- **IGF-1** has insulin-like effects on glucose transport, lowers serum glucose and reduces circulating insulin.

- In patients who are unable to respond to **growth hormone** because of **severe resistance** (caused by GH receptor mutations, postreceptor signaling mutations, or GH antibodies) we use : **recombinant human IGF-I** but it may cause **hypoglycemia** because of its insulinlike effects.

- **Therapeutic Uses of GH** : **replacement therapy** for growth hormone deficiency states.

- **Toxicity & Contraindications in children** : psuedotumor cerebri , Slipped capital femoral epiphysis, Progression of scoliosis during rapid growth , Hypothyroidism.

- **Toxicity & Contraindications in adults** : Carpal tunnel syndrome, Increased activity of cytochrome P450 enzymes, Proliferative retinopathy , Contraindicated in patients with active malignancies.

**\* Mecasermin:**

- Used for **treatment of severe IGF-I deficiency that is not responsive to exogenous GH** which may be caused by mutations in GH receptor and in the GH receptor signaling pathway, neutralizing antibodies to GH, and IGF-I gene defects.

-**Mecasermin** is rhIGF-I alone, administered subcutaneously.

-**Mecasermin rinfabate(higher half life)** is a complex of rhIGF-I and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3).

\* **Most important adverse effect**: Hypoglycemia.

**2) Growth Hormone Antagonists**

**-** Used to **reverse the effects of GH-producing cells** (somatotrophs) in the anterior pituitary that tend to form GHsecreting tumors.

\* Growth hormone excess produces: Acromegaly in adults , Gigantism in children .

**A) Octreotide**(Somatosatin analogs)

**-** Reduce the production of GH

**-** 45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion.

**\* Therapeutic Uses**:

**-** Reduces symptoms caused by a variety of **hormone-secreting tumors**.

**-** secretory, HIV associated, diabetic and chemotherapy or radiation induced **Diarrhea.**

**-** Acute control of bleeding from esophageal varices (important)

**\*** **Adverse effects**: Vitamin B12 deficiency , Biliary sludge and gall stones , Sinus bradycardia.

**B) Bromocriptine**(Dopamine receptor agonists)

**-** Reduce the production of GH

**C) Pegvisomant** (GH receptor antagonists)

**-** Normalizes IGF-1 levels, but does not inhibit GH secretion.

**-** Useful for treatment of **Acromegaly**

**\* Adverse effects:** may lead to increased GH levels and possible adenoma growth.

**Thyroid and Antithyroid Drugs**

- Thyroxine (T4 ) is peripherally metabolized to triiodothyronine (T3 ) by 5'- deiodinase.

**\* Inhibitors of 5'-deiodinase:**

 1. Amiodarone (used in cardiac arrhythmia) 2. Iodinated contrast media 3. Propylthiouracil 4. β-Adrenergic blockers 5. Corticosteroids 6. Severe illness 7. Starvation

**\* Thyroid Hormones (T4 & T3)**

- Absorption is reduced by cholestyramine, ciprofloxacin and aluminum hydroxide.

- Absorption is reduced in severe hypothyroidism (myxedema with ileus) so we switch from oral to pareneteral therapy.

- they bound in the plasma by thyroid binding globulin (TBG).

- Hepatic metabolism is increased by inducers of hepatic microsomal enzymes .In this case, **normal hormone concentration is maintained in euthyroid patients** due to **compensatory hyperfunction of the thyroid gland**, but patients on thyroid replacement therapy require higher doses.

- A similar **compensation** occurs if binding sites are altered: If TBG sites are increased by pregnancy, estrogens, or oral contraceptives, there is an initial shift of hormone from the free to the bound state and a decrease in its rate of elimination until the normal free hormone concentration is restored.

- Affinity of the nuclear receptor for T4 is about 10 times lower than T3.

- **T4(levothyroxine) & T3(liothyronine)** are available for replacement therapy .

- T3 is not recommended for routine replacement therapy because of its shorter half-life (24 hours), requiring multiple daily doses, and difficulty in its monitoring by conventional laboratory tests.

- Synthetic **levothyroxine(T4)** is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity and long halflife (7 days), which permits once-daily to weekly administration.

**\* Antithyroid Drugs**

**1) Thionamides**

**-** Prevention of thyroid hormone synthesis by **inhibiting thyroid peroxidase and blockade of iodine organification**.

- major drugs for treatment of hyperthyroidism.

**\* Methimazole(**given once daily): the drug of choice for hyperthyroidism in adults and children.

**\* Propylthiouracil(**given every 6-8 hours): used during **the first trimester of pregnancy**, in **thyroid storm**, and in those experiencing **adverse reactions to methimazole** (other than agranulocytosis or hepatitis).

- PTU also blocks the peripheral conversion of T4 into T3 by 5'-deiodinase => The effect is slow requiring 3-4 weeks before stores of T4 are depleted.

**- Methimazole and Propylthiouracil** can cross placenta and accumulate in fetal thyroid and cause hypothyroidism, butPropylthiouracil (PTU) less readily so because of high protein binding.

**\* Adverse Effects**: nausea and gastrointestinal distress , Altered sense of taste or smell, Maculopapular pruritic rash, **fatal hepatitis reported with propylthiouracil**, **Cholestatic jaundice is common with methimazole**, **Agranulocytosis (most dangerous**).

**2) Iodides**

- Inhibition of organification and thyroid hormone release, possibly by inhibition of thyroglobulin proteolysis.

- Useful for preoperative preparation for surgery(reduces vascularity, size, fragility of the hyperplastic thyroid glands).

- Should be initiated after onset of thionamide therapy.

- Should be avoided if treatment with 131I is planned.

- Should not be used alone for treatment of hyperthyroidism, because the gland will escape from iodine block in 2-8 weeks.

- Its withdrawal may precipitate thyrotoxicosis because the gland is iodine- enriched.

- Should be avoided during pregnancy, because it may produce fetal goiter

**\* Radioactive Iodine (131I):**

- Major complication is hypothyroidism which requires T4 replacement.

- Should not be administered to pregnant women or nursing mothers.

**3) Iodinated Contrast Media (Ipodate , Iopanoic acid, Iohexol , Diatrizoate)**

- adjunctive therapy in the treatment of thyroid storm.

- Valuable **alternatives** when **iodides or thionamides are contraindicated**.

**4) β-Adrenergic Blockers**

- Those without intrinsic sympathomimetic activity such as **propranolol.**

- Do not typically alter thyroid hormone levels.

- Control tachycardia, hypertension and atrial fibrillation associated with hyperthyroidism.

- In patients with **bronchial asthma** or when **β- adrenergic blockers are contraindicated**, **diltiazem** is an alternative.

**Agents that Affect Bone & Mineral Homeostasis**

**\* Principal regulators of calcium and phosphate homeostasis:**

**1) Parathyroid hormone (PTH)**

**- Calcium limits the production of PTH by:**

a. Calcium-sensitive protease cleaves the intact hormone into fragments.

b. Calcium-sensing receptor (CaSR) is stimulated by calcium, to reduce PTH production and secretion.

- 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 induces the CaSR, making the parathyroid gland more sensitive to suppression by calcium.

- PTH regulates calcium and phosphate flux across cellular membranes in bone and kidney, resulting in increased serum calcium and decreased serum phosphate.

- In bone, PTH increases the activity and number of osteoclasts **indirectly** by acting on the osteoblast to induce membranebound and secreted soluble forms of a protein called RANK .

- RANKL increases both the number and activity of osteoclasts.

-PTH inhibits the production and secretion of sclerostin from osteocytes => blocks osteoblast proliferation.

- Net effect of **excess** endogenous PTH is to increase **bone resorption.**

-Administration of exogenous PTH in **low and intermittent** doses increases **bone formation.**

**-** **Teriparatide**(recombinant PTH 1-34 ): use for treatment of osteoporosis but adequate intake of calcium and vitamin D must be maintained.

**- In the kidney:**

**-** PTH increases tubular reabsorption of calcium

**-** PTH reduces reabsorption of phosphate, amino acids, bicarbonate, sodium, chloride, and sulfate.

- PTH stimulates 1,25(OH)2D production by the kidney.

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

- increases in serum phosphate levels reduce the ionized calcium, leading to enhanced PTH secretion

- Phosphate regulates PTH secretion directly and indirectly by forming complexes with calcium in the serum.

**2) Fibroblast growth factor 23 (FGF23)**

- inhibits 1,25(OH)2D production and phosphate reabsorption in the kidney.

- can lead to both hypophosphatemia and low levels of 1,25(OH)2D.

- 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 with elevated phosphate and 1,25(OH)2D.

- 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**.

- FGF23 binds to FGF receptors 1 and 3c in the presence of an accessory receptor (Klotho).

- Mutations in Klotho disrupt FGF23 signaling, resulting in elevated phosphate and 1,25(OH)2D levels.

- 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.

- High serum phosphate works directly and indirectly by increasing FGF23 levels.

**3) Vitamin D**

- Vitamin D is first hydroxylated in the liver to form 25(OH)D (calcifediol) by CYP2R1.

-25(OH)D (calcifediol) is further converted in the kidney to 1,25(OH)2D (calcitriol) by the enzymes CYP27B1.

- PTH stimulates, and fibroblast growth factor 23 (FGF23) inhibits the production of 1,25(OH)2D by the kidney.

- 1,25(OH)2D is the most potent stimulant of intestinal calcium and phosphate transport and bone resorption.

- 1,25(OH)2D can induce RANKL in osteoblasts and proteins such as osteocalcin, which may regulate the mineralization process.

- 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 1α(OH)D3 increase bone mass and reduce fractures.

- 1,25(OH)2D directly inhibits PTH secretion (independent of its effect on serum calcium) by an effect on PTH gene transcription.

- In patients with chronic renal failure who are 1,25(OH)2D deficient, loss of this 1,25(OH)2Dmediated feedback loop coupled with impaired phosphate excretion and intestinal calcium absorption lead to secondary hyperparathyroidism.

- 1,25(OH)2D also stimulates the production of FGF23.

- Both calcium and phosphate at high levels reduce the amount of 1,25(OH)2D produced by the kidney.

**\* Vitamin D analogs:**

**1. Calcipotriene**: treatment of psoriasis.

**2. Doxercalciferol & paricalcitol**: treatment of secondary hyperparathyroidism in patients with chronic kidney disease.

**3. Eldecalcitol**: in phase 3 clinical trials for the treatment of osteoporosis.

**\* The net effect of:**

- **PTH** is to raise serum calcium and reduce serum phosphate.

-**FGF23** is to decrease serum phosphate.

- **Vitamin D** is to raise serum calcium and serum phosphate.

**\* Secondary Hormonal Regulators of Bone Mineral Homeostasis**

**1) Calcitonin**

- lowers serum calcium and phosphate by actions on bone and kidney.

- inhibits osteoclastic bone resorption.

- increases bone mass and reduces spine fractures

- Calcitonin reduces both calcium and phosphate reabsorption In the kidney.

- 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).

-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**

**2) Glucocorticoids**

**-** alter bone mineral homeostasis by : antagonizing vitamin Dstimulated intestinal calcium transport, stimulating renal calcium excretion, and blocking bone formation.

**-** useful in reversing the hypercalcemia associated with lymphomas and granulomatous diseases such as sarcoidosis or in cases of vitamin D intoxication.

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

**3) 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]2D level in blood, which may result from decreased serum calcium and phosphate and increased PTH.

**-**Men lacking estrogen receptors, or those unable to produce estrogen because of aromatase deficiency, develop marked osteopenia and failure to close epiphysis.

**- Main role is in prevention and treatment of postmenopausal osteoporosis.**

**-**Selective estrogen receptor modulators (SERMs), such as **Raloxifene**, maintain the benefit to bone without increased risk of breast and uterine cancer, and cardiovascular risk.

**-** **Raloxifene** may protect against spine fractures but not those of the hip (bisphosphonates and teriparatide protect against both).

**\* Nonhormonal Agents Affecting Bone Mineral Homeostasis:**

**1. Bisphosphonates** (analogs of pyrophosphate)

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

- They retard formation and dissolution of hydroxyapatite crystals

- potent inhibitors of bone resorption.

- They increase bone mineral density and reduce the risk of fractures in the hip, spine and other locations.

-They inhibit 1,25[OH]2D production. - They inhibit intestinal calcium transport.

-They Inhibit bone cell glycolysis. - They Inhibit bone cell growth.

-The amino bisphosphonates, alendronate, inhibit farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that appears to be critical for osteoclast survival.

**\*Adverse Effects**: Gastric and esophageal irritation, High doses produce mineralization defect and cause renal deterioration and osteonecrosis of the jaw.

**\*Contraindications**: Peptic ulcer disease, esophageal motility disorders.

**\* Therapeutic uses**: Hypercalcemia associated with malignancy, Paget’s disease, Osteoporosis.

2. **Calcimimetics(Cinacalcet)**

- blocks PTH secretion by the activation of calcium sensing receptor(CaSR).

**\* Therapeutic uses:**

1. treatment of secondary hyperparathyroidism in chronic kidney disease.

2. treatment of parathyroid carcinoma.

- **CaSR antagonists** may be useful in hypoparathyroidism or to stimulate intermittent PTH secretion in the treatment of osteoporosis.

3. **Plicamycin (Mithramycin)**

- cytotoxic antibiotic which binds to DNA and interrupts DNA directed RNA synthesis and thus protein synthesis.

**\* Therapeutic uses:** treatment of Paget’s disease and hypercalcemia

4. **Thiazides Diuretics**

- Reduce renal calcium excretion.

- Decrease urine oxalate excretion and increase urine magnesium and zinc levels, both of which inhibit calcium oxalate stone formation.

**\* Therapeutic uses** :Indicated for hypercalciuria and stone formation in patients with idiopathic hypercalciuria

5. **Denosumab**

- Human monoclonal antibody that binds to and prevents the action of RANKL.

- inhibits osteoclast formation and activity.

**\* Adverse Effects:** **Increased risk of infection**, **transient hypocalcemia** especially in patients with marked bone loss or compromised calcium regulatory mechanisms, including chronic kidney disease and vitamin D deficiency.

**\* Therapeutic uses** :

1.treatment postmenopausal osteoporosis.

2. treatment of 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.

6. **Strontium Ranelate**

- blocks differentiation of osteoclasts while promoting their apoptosis, thus inhibiting bone resorption and promotes bone formation.

- Unlike bisphosphonates, denosumab, or teriparatide, this drug **increases bone formation markers while inhibiting bone resorption markers.**

**Antidiabetic Drugs**

**I. Insulin (type 1 DM)**

- **Glucocorticoids** lower the affinity of insulin to its receptors.

- Aberrant serine and threonine phosphorylation of β subunits or insulin receptor substrates( IRS) molecules may result in insulin resistance and functional receptor down regulation.

- **Drugs which stimulate Insulin Secretion** : sulfonylureas, meglitinide, nateglinide, isoproterenol, and acetylcholine.

- **Drugs which inhibit Insulin Secretion** : diazoxide, phenytoin, vinblastine, and colchicine.

**\* Types of Insulin Preparations:**

**1. Rapid-acting insulin (very fast onset & short duration):**

**-** allow insulin to be taken immediately before the meal without sacrificing glucose control.

- have the lowest variability of absorption of all available commercial insulins

**- Their duration of action is rarely more than 4- 5 hours, which decreases the risk of late postmeal hypoglycemia**

- preferred for use in continuous subcutaneous insulin infusion devices.

 **A. Insulin lispro**

**(**proline at position B28 has been moved to B29, and lysine at position B29 has been moved to B28)

**-** The advantage of this analog is its very low propensity – in contrast to human insulin – to self-associate in antiparallel fashion and form dimers.

**B. Insulin aspart**

**(**substituted B28 proline with a negatively charged aspartic acid.)

**C. Insulin glulisine**

(formulated by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29)

**2. Short-acting insulin (rapid onset): (Regular Insulin)**

**-** It is a short-acting soluble crystalline zinc insulin made by recombinant DNA technique.

**- Effects appear within 30 min, peak 2-3 hours after sc injection and last for 5-8 hours.**

**- it should be injected 30-45 minutes before meals**

**-** This is the only type of insulin that should be administered IV in the management of diabetic ketoacidosis

**-** If administered at meal times, blood glucose rises faster than insulin=> **early postprandial hyperglycemia** and an increased risk of late postprandial hypoglycemia.

**\* Rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amount of zinc to increase their stability and shelf-life.**

**3. Intermediate-acting and Long-acting insulins**

**A. NPH (neutral protamine Hagedorn, or isophane insulin ).**

**-** intermediate-acting insulin

**- Onset of action 2-5 hours and duration of 4- 12 hours.**

**-** Can be mixed with regular, lispro, aspart or glulisine insulin.

**-** Dispensed as turbid suspension at neutral pH with protamine in phosphate buffer.

**B. Insulin glargine**

**-** It is a soluble, “peakless”, and “long-acting” insulin analog.

**-** Dispensed as clear solutions.

**- Onset of action 1-1.5 hours, peak effect( not a true peak) occurs at 4-6 hours and maximal activity is maintained for 11-24 hours or longer.**

**-** Should not be mixed with other insulins.

**C. Insulin detemir**

(terminal threonine is dropped from the B30 position and myristic acid (FA) is attached to the terminal B29 lysine.)

- Its use is associated with less hypoglycemia than NPH insulin.

**- Onset of action is dose dependent, 1-2 hours, and duration of action of more than 24 hours.**

-Dispensed as clear soluble solution.

**4. Mixtures of insulin**

**-** intermediate-acting insulins (NPH) require several hours to reach adequate therapeutic levels so their use in type 1 diabetic patients require supplements of rapid- or short-acting insulin before meals.

- Insulin glargine and detemir must be given as separate injections. They are not miscible acutely or in a premixed preparations with any other insulin preparation.

**\* Insulin Delivery Systems:**

 1. The standard mode is **subcutaneous injection** using conventional disposable needles and syringes.

2. **Portable pen injectors**: prefilled, with replaceable needles.

 3. **Continuous subcutaneous insulin infusion devices** (pumps).

 4. **Inhaled insulin**:

**- Peak levels are reached in 12 -15 minutes and decline to baseline in 3 hours, faster in onset and shorter in duration than subcutaneous insulin.**

- Adverse effects include cough.

-Contraindicated in smokers and patients with chronic obstructive pulmonary disease.

**\*Complications of Insulin Therapy:**

**1) Hypoglycemia**: is the most common and serious complication.

-Manifested by signs of autonomic hyperactivity, both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger), which may progress to convulsions and coma if untreated.

- Frequent hypoglycemic episodes during tight glycemic control, lead to “hypoglycemic unawareness”.

- All the manifestations of hypoglycemia are relieved by glucose administration.

**2. Immune disorders:**

A. Insulin allergy: immediate type hypersensitivity reaction, anaphylaxis, IgE-mediated. Mainly due to noninsulin protein contaminants.

B. Immune insulin resistance: IgG anti-insulin antibodies neutralize action of insulin.

**3. Lipodystrophy at injection sites:** **Hypertrophy** of subcutaneous fatty tissue at sites of repeated injections.

**II. Oral antidiabetic agents (type 2 DM)**

 **A. Insulin secretagogues:**

**1. Sulfonylureas**

**-** they bind to their receptor which is associated with B cell ATP-sensitive K+ channel which inhibits the efflux of K+ ions through the channel resulting in cell depolarization and opening of voltage-gated Ca2+ channel and calcium influx and the release of preformed insulin.

**-** The longer the half-life, the more likely is the hypoglycemia.

**-** Potentiated by sulfonamides, clofibrate, dicumarol, salicylates and phenylbutazone (competition for protein binding) and alcohol (malnutrition).

**a) First-generation sulfonylureas(Tolbutamide, Chlorpropamide, Tolazamide)**

**b) Second-generation sulfonylureas**

**b.1) Glipizide**

**- Have the shortest half-life of the potent agents (2-4 hours).**

**- should be ingested 30 min before breakfast to reduce postprandial hyperglycemia.**

- Contraindicated in patients with significant hepatic impairment and renal insufficiency.

- Cause Disulfiram-like reaction, Hyponatremia by potentiating effects of ADH, chlorpropamide.

**b.2) Glimepiride**

**-** Most potent sulfonylurea.

**-** Given once daily, t½ of 5 hours.

**b.3) Glyburide (glibenclamide)**

**-** contraindicated in the presence of hepatic impairment and in renal insufficiency.

**b.4) Gliclazide**

**-** It has a half-life of 10 hours

 **2. Meglitinides**

**a) Rapaglinide& Mitiglinide**

**-** Very fast onset of action with peak effect at 1 hour after ingestion, and a duration of action of 4-7 hours.

**-** Metabolized by CYP3A4 **-** Indicated for control of postprandial hyperglycemia

**-** can be used in patients with renal impairment and in the elderly.

**-** There is no sulfur in its structure, so it may be used in type 2 diabetics with sulfur or sulfonylurea allergy.

**b) Nateglinide (**D-Phenylalanine Derivative**)**

**-** stimulates very rapid and transient release of insulin from B cells through closure of the ATPsensitive K+ channels.

**- absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour and an overall duration of action is about 4 hours.**

**-** metabolized in the liver by CYP2C9 and CYP3A4 with a half-life of about 1 hour.

**-** Hypoglycemia is the main adverse effect.

- It can be used in patients with renal impairment and in the elderly.

 **B. Biguanides (Metformin) => important**

**-** blood-glucose lowering action does NOT depend on functioning pancreatic B cells.

**-** produces less fasting hyperglycemia as well as less postprandial hyperglycemia.

**-** Euglycemic agents

**-** The primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic glucose production.

**-** It is an insulin-sparing agent, does not increase body weight or provoke hypoglycemia.

**-** The first-line therapy for type 2 diabetes.

- It is most often prescribed for (insulin resistance) syndrome.

- It decreases the risk of macrovascular as well as microvascular disease

- It is useful in the prevention of type 2 diabetes in middle-aged obese patients with impaired glucose tolerance and fasting hyperglycemia, but not in older, leaner prediabetics

- Metformin therapy should therefore be temporarily halted on the day of radiocontrast use and restarted a day or two later after confirmation that renal function has not deteriorated.

**\* Adverse Effects :**

1) Gastrointestinal: anorexia, nausea, vomiting, abdominal discomfort, diarrhea

2) Reduction of vitamin B12 levels during longterm therapy (Increased intake of calcium may prevent the metformin-induced B12 malabsorption).

3) Lactic acidosis in the presence of hypoxia and renal or hepatic insufficiency

**C.Thiazolidinediones**

**-** euglycemic

**-** reduce insulin resistance

**-** The last choice of the treatment of type 2 diabetes.

**-** They act as ligands to (Peroxisome proliferatoractivated receptor-gamma, PPAR-γ).

**-** Promote fatty-acid uptake and storage in adipose tissue rather than skeletal muscle or liver, which makes them more sensitive to insulin.

**-** Suppress glucose production in the liver.

**-** Have a slow onset and offset of activity over weeks or months, because their mechanism of action involves gene regulation.

**-** Restricted to patients who remain hyperglycemic despite taking other antidiabetic medications.

**1) Pioglitazone**

**-** Metabolized by CYP2C8 & CYP3A4 to active metabolites.

**-** It lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol

**-** reduces neointimal proliferation after coronary stent placement (positive effect on endothelial function).

**-** Increased risk of bladder cancer with increased dosage and duration of pioglitazone use.

**2) Rosiglitazone**

**-** Metabolized mainly by CYP2C8 to minimally active metabolites.

**-** It increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides.

**-** reduce microalbuminuria

**-** New or worsening macular edema with rosiglitazone. Improves when drug is discontinued.

**\* These drugs have been shown to improve the biochemical and histologic features of nonalcoholic fatty liver disease.**

**\* Adverse Effects**: Fluid retention , Dose-related weight gain , Loss of bone mineral density

\* Should not be used during pregnancy, in the presence of liver disease, in the presence of heart failure.

\*Anovulatory women may resume ovulation which lead to pregnancy.

(يمكن أن يؤدي الى حدوث حمل في النساء اللواتي تجاوزن سن اليأس)

 **D. α-Glucosidase inhibitors)** **Acarbose and Miglito**l **(**

**-**competitive inhibitors of intestinal α- glucosidases: sucrase, maltase, glycoamylase, dextranase.

**-** **Miglitol** is 6 times more potent than acarbose.

**-Miglitol** alone inhibits isomaltase and β- glucosidases.

- **Acarbose** alone inhibits α-amylase

- **Reduce postprandial hyperglycemia** and delaying absorption of sugars to distal segments of the intestine, thus having insulin sparing action.

- Can prevent type 2 diabetes development in prediabetics.

- Reduce cardiovascular disease and hypertension.

**\* Adverse Effects:**

1) Flatulence, diarrhea and abdominal pain

2) Hypoglycemia with combination therapy which should be treated with glucose and NOT sucrose.

**\* Contraindications**: patients with renal insufficiency , nflammatory bowel disease or GI diseases, hepatic disease.

**III. Others:**

 **A. Amylin Analogues (Pramlintide)**

**- It is rapidly absorbed after subcutaneous administration; levels peak within 20 minutes, and the duration of action is not more than 150 minutes.**

- Slow gastric emptying – vagally mediated. - Reduce glucagon secretion.

 - Promote satiety or reduce appetite - centrally. - Produces moderate weight loss.

- Given by subcutaneous injection before meals.

- Used in type 1 DM, and type 2 DM unable to achieve their target postprandial blood glucose levels.

- cannot be mixed with insulin

**\* Adverse effects**: Hypoglycemia: concurrent rapid- or short-acting mealtime insulin dosages should be decreased by 50% or more.

 **B. GLP-1 – based “incretin” therapies**

**1. GLP-1 analogues** (**Exenatide**, liraglutide, albiglutide, and dulaglutide):

**\* Exenatide**

**-** Used as **adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.**

**-** It is injected subcutaneously within 60 minutes before breakfast and dinner.

**- It peaks in ~ 2 hours with a duration of action of up to 10 hours.**

**-** Suppresses appetite and Associated with weight loss.

**-** Not associated with hypoglycemia unless used in combination.

**\* Adverse effects**: major adverse effect is nausea , Acute pancreatitis

**2. DPP-4 inhibitors (sitagliptin**, saxagliptin, linagliptin, vildagliptin, and alogliptin**)**

**\* Sitagliptin**

**-** used in combination with a TZD or metformin, or sulfonylureas

**- Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.**

**-** Dosage should be reduced in patients with impaired renal function.

**- don’t cause weight gain or loss**

**\* Adverse effects:** Nasopharyngitis, upper respiratory infections, headaches , Hypoglycemia when the drug is combined with insulin secretagogues or insulin.

**-** Not associated with hypoglycemia when used alone

**C. Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors.** (**canagliflozin**, dapagliflozin, and empagliflozin)

**- increase urinary glucose loss.**

**-** contraindicated in chronic renal dysfunction.

**\* Adverse effects**: Increased incidence of genital and urinary tract infections, Higher rates of breast cancer and bladder cancer.

**Adrenocorticosteroids**

**1. glucocorticoids**

- Its Secretion is controlled by the pituitary release of corticotropin (ACTH).

-Synthetic steroids like **dexamethasone** are largely bound to albumin rather than to corticosteroid-binding globulin(CBG)

- The effects of glucocorticoids are mainly due to proteins synthesized from mRNA transcribed by their target genes.

- Some of the glucocorticoids effects can be attributable to binding to aldosterone receptors (ARs). ARs bind aldosterone and cortisol with similar affinity, while cortisone has minimal affinity for ARs.

**\* Permissive actions of glucocorticoids :**

1. The response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol and is restored by physiological amounts of it.

2. Lipolytic responses of fat cells to catecholamines, ACTH and GH are attenuated in the absence of glucocorticoids.

 3. In the absence of cortisol, glomerular filtration is impaired, vasopressin (ADH) secretion is augmented and the ability to excrete water load is abolished.

**\* Dose-dependant Actions of glucocorticoids:**

**a. Metabolic effects**

1) Stimulate and are required for gluconeogenesis and glycogen synthesis in the fasting state.

2) Stimulate the release of amino acid during muscles catabolism.

3) Increase serum glucose levels and thus insulin release.

4) Inhibit glucose uptake by muscles 5) Stimulate lipase and thus lipolysis.

**b. Catabolic effects**

they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat and skin, leading to:

1. Decreased muscle mass 2. Thinning of the skin. 3. Osteoporosis. 4. Reduced growth in children.

**c. Antiinflammatory and immunosuppressive effects**

- Glucocorticoids dramatically reduce the manifestations of inflammation due to their **profound effects** on the concentration, distribution, and function of peripheral leukocytes and to their **suppressive effects** on the inflammatory cytokines and chemokines and on other mediators of inflammation.

- After a single dose of a short-acting glucocorticoid, the concentration of neutrophils in the circulation increases while the lymphocytes (T and B cells), monocytes, eosinophils, and basophils decrease.

- The increase in neutrophils is due both to the increased influx into the blood from the bone marrow and to the decreased migration from the blood vessels.

- The reduction in circulating lymphocytes, monocytes, eosinophils, and basophils is primarily the result of their movement from the vascular bed to lymphoid tissue.

- Glucocorticoids inhibit the functions of tissue macrophages and other antigen-presenting cells.

- Glucocorticoids Inhibit phospholipase A2.

- Glucocorticoids Reduce expression of cyclooxygenase-2.

- Glucocorticoids Reduce mast cell degranulation and histamine release.

- Glucocorticoids used to control transplant rejection.

- The anti-inflammatory and immunosuppressive effects of Glucocorticoids are responsible for some of their most serious adverse effects.

**d. Other effects**

1) Adrenal insufficiency

2) behavioral disturbances: initially insomnia and euphoria and subsequently depression.

3) pseudotumor cerebri

4) Glucocorticoids given chronically suppress the pituitary release of ACTH, GH, TSH, and LH.

5) Redistribution of fat

6) Peptic ulceration

7) Antagonizes the effects of vitamin D on Ca2+ absorption

8) Increases the number of platelets and RBCs

9) Development of fetal lung and formation of surfactant

10) Cortisol deficiency results in impaired renal function , augmented vasopressin secretion, and diminished ability to excrete a water load.

**\* Synthetic Corticosteroids (you have to memorize the table)**

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**\* Therapeutic Uses:**

**1. Diagnosis and treatment of disturbed adrenal functions:**

**1) Adrenocortical insufficiency: a. acute b. chronic (Addison’s disease)**

- Replacement therapy with **hydrocortisone + mineralocorticoid (fludrocortisone)**.

- Synthetic glucocorticoids that are long-acting and devoid of salt-retaining activity should not be administered to these patients(**Meprednisone,triamcinolone,paramethasone,fluprednisolone,betamethasone,dexamethasone) <= very important .**

**2) Adrenocortical hypo- and hyperfunction:**

a. Congenital adrenal hyperplasia: The aim is to suppress ACTH production.

b. Cushing’s syndrome: Replacement therapy with large doses of **hydrocortisone** following surgical treatment of Cushing’s syndrome.

c. Primary generalized glucocorticoid resistance (Chrousos syndrome): A rare, genetic condition due to inactivating mutations of the glucocorticoid receptor gene => high doses of synthetic glucocorticoids such as **dexamethasone** with no inherent mineralocorticoid activity.

**2. Dexamethasone suppression test for differential diagnosis of Cushing’s syndrome.**

**3. Stimulation of lung maturation in the fetus:** by administration of **betamethasone** to the mother when premature delivery is anticipated which reduce incidence of respiratory distress syndrome (RDS).

**4. Treatment of Non-adrenal disorders:**

**-** Corticosteroids are not usually curative, thus, the pathologic process may progress while clinical manifestations are suppressed.

**-** Glucocorticoid therapy can reactivate dormant tuberculosis.

**-** The presence of diabetes, peptic ulcer, osteoporosis, and psychological disturbances should be taken into consideration.

**\* Adverse Effects:**

**1)** iatrogenic Cushing’s syndrome after 2 weeks of therapy(Major undesirable effect)

**2)** Na+ and water retention and K+ and H+ loss:

a. hypokalemic hypochloremic alkalosis.

b. hypertension in patients with normal cardiovascular and renal function.

c. edema in patients with hypoproteinemia, renal disease, hepatic disease.

 d. congestive heart failure in patients with cardiovascular disease.

- Can be prevented by choosing synthetic, non-salt retaining steroids (**Meprednisone,triamcinolone,paramethasone,fluprednisolone,betamethasone,dexamethasone)** or Na+ restriction and K+ supplements.

3) Suppression of the hypothalamic-pituitaryadrenal axis (Adrenal suppression):

- Occurs when corticosteroids are used for more than 2 weeks.

 - If corticosteroid therapy is to be terminated, this should be done gradually (**tapering**) to allow recovery of the axis.

- Alternate-day therapy can avoid suppression of the hypothalamic-pituitary-adrenal axis.

- Symptoms of hypoadrenalism in the presence of normal cortisol levels indicate glucocorticoid dependence.

**2. Mineralocorticoids**

- Salt retaining hormones.

**A) Natural: Aldosterone, Deoxycorticosterone**

- The major effect of activation of aldosterone receptor is increased expression of Na+ / K+ ATPase and the epithelial sodium channel (ENaC).

- Aldosterone is mainly under regulation by angiotensin and only partially by ACTH.

- Deoxycorticosterone secretion is primarily under the influence of ACTH (in contrast to aldosterone).

**b) Synthetic: Fludrocortisone**

- Potent steroid with both glucocorticoid and mineralocorticoid activity.

- The most commonly prescribed salt-retaining hormone

**\* Therapeutic Uses:** treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency.

**\*Mineralocorticoid Antagonists:**

 **1. Spironolactone**

- aldosterone receptor competitive antagonist.

-also an androgen antagonist, used in the **treatment of hirsutism in women**.

- used in the treatment of primary aldosteronism, and also in its diagnosis in hypokalemic patients with hypertension and used as a diuretic in heart failure

- **Adverse effects**: hyperkalemia, cardiac arrhythmia, menstrual abnormalities, gynecomastia, sedation, headache, gastrointestinal disturbances, and skin rashes.

**2. Eplerenone**

- aldosterone receptor antagonist.

- treratment of hypertension and It reduces mortality in heart failure like spironolactone.

- most common toxicity is hyperkalemia

**3. Drospirenone**

- Is a progestin used in oral contraceptives

- Antagonizes the effects of aldosterone.

**3. Androgenic(Dehydroepiandrosterone (DHEA) sulfate) or estrogenic activity(androstenedione)**