**Hypothalamic & Pituitary Hormones**

**1) Growth Hormone (Somatotropin)**

- 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

**\* Mecasermin/ Mecasermin rinfabate:**

- Used for **treatment of severe IGF-I deficiency that is not responsive to exogenous GH.**

**2) Growth Hormone Antagonists**

**A) Octreotide**(Somatosatin analogs):

**-** Reduce the production of GH.

**-** 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).

**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**

**Thyroid and Antithyroid Drugs**

**\* 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.

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

- 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).

**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.

**\* 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)**

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

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

- 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**.

**3) Vitamin D**

**\* 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**

-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**

**-** 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**

**- 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**).

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

2. **Calcimimetics(Cinacalcet)**

**\* 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.

**\* 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**

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

**Antidiabetic Drugs**

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

- **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**

**A. Insulin lispro**

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

**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.**

**B. Insulin glargine**

**- 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.**

**4. Mixtures of insulin**

- 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.

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

 **A. Insulin secretagogues:**

**1. Sulfonylureas**

**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.**

- 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.

**-** 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**)**

**- 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.**

- 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.

**C.Thiazolidinediones**

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

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

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

**1) Pioglitazone**

**-** 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**

**-** reduce microalbuminuria

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

**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.

  **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.**

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

- cannot be mixed with insulin

 **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.

**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.**

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

**- increase urinary glucose loss.**

**-** contraindicated in chronic renal dysfunction.

**Adrenocorticosteroids**

**1. glucocorticoids**

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

**\* 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).

**\* Adverse Effects:**Na+ and water retention and K+ and H+ loss: Can be prevented by choosing synthetic, non-salt retaining steroids (**Meprednisone,triamcinolone,paramethasone,fluprednisolone,betamethasone,dexamethasone)** or Na+ restriction and K+ supplements.

**2. Mineralocorticoids**

**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**

- 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

**2. Eplerenone**

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

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