Diabetes mellitus (D.M.):

Is a group of metabolic diseases in which there is deficient insulin secretion or decreased sensitivity of insulin receptors on target cells, resulting in hyperglycemia.

Types of D.M.:

1. Type 1
2. Type 2
3. Gestational diabetes

Anti-diabetic Drugs

A- Insulin: for type 1 DM

Insulin Preparations

Type	Onset (How quickly it starts working)	Peak (When it is most effective)	Duration (How long it works)	Timing of Injection (When it should be given)
Bolus insulins				
Rapid-acting analogues aspart (Novorapid), glulisine (Apidra), lispro (Humalog)	10–15 minutes	1–2 hours	3–5 hours	Given with one or more meals per day. To be given 0–15 minutes before or after meals.
Short-acting Humulin R/Novolin ge Toronto	30 minutes	2–3 hours	6.5 hours	Given with one or more meals per day. Should be injected 30–45 minutes before the start of the meal.
Basal insulins				
Intermediate-acting Humulin N/NPH	1–3 hours	5–8 hours	Up to 18 hours	Often started once daily at bedtime. May be given once or twice daily. Not given at any time specific to meals.
Long-acting analogues Glargine (Lantus) Detemir (Levemir)	90 minutes	Not applicable	Lantus: Up to 24 hours Levemir: 16–24 hours	Often started once daily at bedtime. Levemir may be given once or twice daily. Not given at any time specific to meals.
Premixed insulins				
Premixed regular insulin Humulin 30/70 and Novolin ge 30/70, 40/60, 50/50	Varies according to types of insulin	Contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin). See above for information on peak actions based on insulin contained.		Given with one or more meals per day. Should be injected 30–45 minutes before the start of the meal.
Premixed insulin analogues NovoMix 30 and Humalog Mix 25, Mix 50	Varies according to types of insulin			Given with one or more meals per day. Should be injected 0–15 minutes before or after meals.

ACTION: promote the entry of glucose into cells

B- Oral Agents: for type 2 DM

They are useful for type 2 DM that cannot be managed by diet alone.

Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents.

Notes: long-standing DM may require a combination of oral agents with or without insulin.

Oral glucose-lowering agents include:

(1) Insulin secretagogues
(2) Insulin sensitizers
(3) α- Glucosidase inhibitors
(4) Dipeptidyl peptidase-IV inhibitors
(5) Sodium–glucose cotransporter 2 inhibitors
(6) Others.

1. Insulin secretagogues

(Sulfonylureas & Glinides)

They promote insulin release from pancreas, so their action depend on functioning pancreatic β cells.

A. Sulfonylureas (SUs)

Include the 1st generation (**Tolbutamide**) & 2nd generation drugs (**Glyburide "Glibenclamide"**, **Glipizide** & **Glimepiride**).

MOA:

1) Block ATP-sensitive K+ channels, resulting in depolarization & Ca2+ influx, & insulin exocytosis.
2) Reduce hepatic production of glucose & increase peripheral sensitivity to insulin.

Kinetics:

- Bind to serum proteins, excreted in the urine and feces.
- **Duration of action** is the shortest for **tolbtamide** (6-12 hours), while that of 2nd generation is ranged from 12 to 24 hours.

Adverse effects:

- Weight gain, hyper-insulinemia & hypoglycemia.
- Used with caution in patients with hepatic or renal insufficiency.
- **Glyburide** is metabolized to active compounds**,** thus glipizide or glimepiride are safer options in renal dysfunction and in elderly.
- **Glyburide** has minimal transfer across the placenta, and it may be an alternative to insulin for DM during pregnancy.

Drug interaction:

1- Atypical antipsychotic, Corticosteroids, Diuretics, Niacin, Phenothiazines.
2- Azole antifungals, Beta-blockers, Chloramphenicol, Clarithromycin, Monoamine oxidase inhibitors, Probenecid, Salicylates & Sulfonamides potentiate **SUs** effects.

B. Glinides

Repaglinide & **Nateglinide**.

MOA:

- Bind to a distinct site on the SUs receptor of ATP-sensitive potassium channels.
- In contrast to SUs, glinides have a rapid onset & a short duration of action.

Effective in the early release of insulin occurs after a meal & are categorized as postprandial glucose regulators. Glinides should be taken prior to a meal.

- glinides should not be used in combination with **SUs** due to overlapping Mechanisms of action which increase the risk of serious hypoglycemia.

Adverse effects:

- Incidence of hypoglycemia & weight gain is lower than that with SUs.
- **Repaglinide** effect may be enhanced by ketoconazole, itraconazole, fluconazole, erythromycin & clarithromycin, whereas decreased by barbiturates, carbamazepine & rifampin.
- Concurrent use of **repaglinide** with **gemfibrozil** (lipid-lowering drug) is contraindicated because the later inhibits hepatic metabolism resulting in severe hypoglycemia.
- Used cautiously in patients with hepatic impairment.

2. Insulin sensitizers (Biguanides & Thiazolidinediones)

They improve target-cell response to insulin without increasing insulin secretion.

A. Biguanides: Metformin

- The only currently available biguanide.
- It increases glucose uptake & use by target tissues, decreasing insulin resistance.

MOA:

1. The main mechanism is the reduction of hepatic gluconeogenesis (**Note**: In type 2 DM excess glucose produced by the liver is a major source of hyperglycemia, accounting for fasting hyperglycemia).
2. Slows intestinal absorption of sugars, improving peripheral glucose uptake & utilization.

- Weight loss due to appetite loss.
- recommended as the initial drug of choice for type 2 DM.
- Used alone or in combination with other oral agent or insulin.

- Hypoglycemia may occur when **metformin** is taken with insulin or insulin secretagogues (dose adjustment may be required).

Adverse effects:

- Largely are gastrointestinal.
- **Metformin** is contraindicated in presence of renal dysfunction due to the risk of lactic acidosis.
- It should be discontinued in cases of acute MI, exacerbation of HF, sepsis, or other disorders that can cause acute renal failure.
- Used cautiously in old patients (< 80 years) & in those with a history of HF or alcohol abuse.
- Should be temporarily discontinued in patients undergoing diagnosis requiring IV radiographic contrast agents.
- Long-term use may interfere with vitamin B12 absorption.

B. Thiazolidinediones (TZDs) (glitazones)

- No risk of hyperinsulinemia.
- Include glitazones pioglitazone & Rosiglitazone.

MOA:

- Act as agonists on peroxisome proliferator–activated receptor-γ (PPARγ), a nuclear hormone receptor, thus, increase sensitivity to insulin in adipose tissue, liver & skeletal muscle.
- Hyperglycemia, hyperinsulinemia, hypertriglyceridemia & elevated HbA1c levels all are improved.
- **Rosiglitazone** increases LDL cholesterol & triglycerides, whereas **pioglitazone** decreases triglycerides.
- Both drugs increase HDL levels.
- **TZDs** are used as monotherapy or in combination with other oral agents or insulin (insulin dose should be lowered).
- **Pioglitazone** is recommends as a 2^{nd} or 3^{rd} line alternative for patients who fail or have contraindications to **metformin** therapy.
- **Rosiglitazone** is not recommended because of the cardiac adverse effects.

Adverse effects:

- Liver function monitoring is recommended because liver toxicity was reported with the use of these drugs.
- Weight gain possibly because TZDs may increase SC fat & cause fluid retention (which can worsen HF), thus TZDs should be avoided in patients with severe HF.
- Osteopenia & increased fracture risk may occur with TZDs use.
- **Pioglitazone** may increase bladder cancer risk.
- The risk of MI & death restricts **rosiglitazone** use.

3. α- Glucosidase inhibitors : Acarbose & Miglitol

MOA:

- They reversibly inhibit α-glucosidase enzymes (in the intestinal brush border), if these drugs are taken at the start of a meal they delay carbohydrates break down into glucose & other simple sugars, thus lowering postprandial glucose levels.
- **Acarbose** also inhibits pancreatic α-amylase, thereby interfering with the breakdown of starch into oligosaccharides.
- Do not cause hypoglycemia, but their combination with insulin secretagogues or insulin may cause hypoglycemia which should be treated with glucose rather than sucrose (because sucrose is also inhibited).

Adverse effects:

- Flatulence, diarrhea & abdominal cramping.
- Should not be used in the presence of inflammatory bowel disease, colonic ulceration, or intestinal obstruction.

4. Dipeptidyl peptidase - IV (DPP-4) inhibitors: Alogliptin, Linagliptin, Saxagliptin & Sitagliptin

MOA: Inhibit DPP-4 enzyme preventing the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1), increasing insulin release in response to meals & reduce inappropriate secretion of glucagon.

- Used as monotherapy or combined with SU, metformin, TZDs or insulin.
- Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.

Adverse effects:

- Nasopharyngitis, headache & pancreatitis.
- Ritonavir, atazanavir, itraconazole, and clarithromycin, may inhibit **saxagliptin**

metabolism.

5. Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors: Canagliflozin & Dapagliflozin

MOA:

- Inhibit SGLT2 (which reabsorbs filtered glucose in the kidney), decreasing glucose reabsorption & increasing its excretion.
- Also sodium reabsorption is decreased resulting in osmotic dieresis, that may reduce systolic BP, though, SGLT2 inhibitors are not indicated for HT treatment.

Adverse effects:

- Genital mycotic infections in female (e.g., vulvovaginal candidiasis), UTIs, and urinary frequency.
- Hypotension, occurred, in elderly or patients on diuretics (evaluate volume status before treatment).

6. **Other agents:** **Bromocriptine** and **colesevelam** (bile acid sequestrant) cause modest reductions in HbA1c by unknown mechanism.

- Their clinical use for treatment of type 2 DM is limited by their modest efficacy, adverse effects, and pill burden.