Diabetes mellitus (DM):

- Common metabolic disorder.
- Due to Insulin deficiency or resistance

Pathophysiology of Diabetes:

- Insulin deficiency/resistance leads to: Hyperglycemia (increased blood glucose level) → Glycosuria (glucose crosses the renal threshold and excreted in urine) → Polyuria (excessive urination as glucose being osmotically active holds water with it) → Polydipsia (excessive thirst due to water loss) → Polyphagia (increased appetite due to glucose deficiency) and Weight loss (altered fat metabolism).
- There is extracellular glucose excess but intracellular deficiency, known as **starvation in the midst of plenty**.
- Impaired CHO metabolism leads to utilization of more fats resulting in formation of ketone bodies (**ketosis**).
- High acidic ketone bodies → **Acidosis.**

Coma in DM:

1. **Ketoacidotic coma** – Characterised by Ketosis, and increased formation of of Na and K salts of ketoacids. There loss of salts in urine, rapid and deep ketotic breath with fruity ketotic odor, and vomiting. Associated increased respiratory rate is known as Kussmaul respiration.

2. **Hyperosmolar coma** - Pl. glucose>600 mg/dl (increase in blood osmolarity to >320 mOsm/kg) → water is drawn out of the cells → water loss and glucosuria → → dehydration. Progressive dehydration in the cells as water is taken from them and excreted. Electrolyte imbalances are also common. It is also known as Hyperosmolar hyperglycemic non-ketotic syndrome. Non-ketotic coma is usually precipitated by an infection, myocardial infarction, stroke or another acute illness. Ketosis is not seen as the presence of some insulin inhibits hormone-sensitive lipase mediated fat tissue breakdown.

3. **Severe hypoglycemic coma** – Seen if insulin or oral hypoglycemic drugs (OHG) drugs are incorrectly timed, if there is over/incorrectly-timed exercise, enough food is not taken with insulin and OHG drugs. Clinical features include agitated, sweaty, weak patient with symptoms of sympathetic activation. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death.

Chronic complications of DM

<u>Microvascular:</u>

- Retinopathy
- Neuropathy
- Nephropathy

<u>Macrovascular:</u>

- Cerebrovascular Disease
- Peripheral Vascular Disease
- Coronary Heart Disease

Mechanism of chronic complications:

1. Increased production of advanced glycation end products (AGE) as a result of chronic hyperglycemia. Exposure to elevated glucose results in bonding of glucose with amino acids and the formation of reversible Amadori products (Maillard Reaction). Amodori products progress to stable covalent adducts known as AGE. AGEs lead to activation of signaling cascades, elevated production of reactive oxygen species, and abnormal stimulation of hemodynamic regulation systems like RAAS. AGEs also form cross link with matrix proteins, thus damaging blood vessels. AGEs also interfere with the leucocyte response to infections.
2. Increased intracellular glucose in insulin indepdendent tissues→aldose reductase activation→sorbitol formation→decreased Na^+ K^+ ATPase.

Types of Diabetes:

	Type I (juvenile onset/insulin dependent DM)	Type II (adult onset/non-insulin dependent DM)
1.	Insulin deficiency	Insulin resistance.
2.	Plasma insulin is low.	Pl. insulin nprmal or elevated.
3.	Age of onset - <40yrs.	>40 yrs of age.
4.	Patients are not obese, have high incidence of ketosis & acidosis.	Obese patients, insidious onset, rarely associated with ketosis. Hyperosmolar coma is common.
5.	Concordance rate in identical twins is 33%.	Stronger genetic component, 100% concordance rate.

WHO criteria for diagnosis of DM -

1. Fasting Plasma Glucose >126 mg/dl (Fasting is defined as no caloric intake for at least 8 h).
2. Post-prandial plasma glucose > 200 mg/dl
3. In a patient with classic symptoms of hyperglycemia, a random Plasma glucose >200 mg/dl
4. HbA1c > 6.5%