Diabetes Mellitus

DR PIYUSH TAILOR
ASSOCIATE PROFESSOR
GOVT. MEDICAL COLLEGE
SURAT

What is diabetes?

- Group of diseases
- High levels of blood glucose
- Due to defects in insulin production
- Due to defects in insulin action
- Both.

- Metabolic disorder
- Chronic hyperglycaemia
- Disturbances of carbohydrate, fat and protein metabolism

Diabetes – Clinical Features

Commom Representation

- Polyuria
- Polyphagia
- Polyuria
- Weight loss.
- Blurring of vision

Severe forms

- Ketoacidosis
- Non–ketotic hyperosmolar state

Later Symptoms

- Fatigue
- Dry skin
- Recurrent infection
- Feet Ulceration
- Sensory loss in lower extremities
- Erectile dysfunction
- Slow Healing of wounds
- Visual disturbance

Types of Diabetes

- **Type 1 Diabetes Mellitus**
- **Type 2 Diabetes Mellitus**
- **Gestational Diabetes**
- Other types:
  - **LADA** (Latent Autoimmune Diabetes of Adult onset)
  - **MODY** (Maturity Onset Diabetes of Young)
    - Mutation in Gene
  - **Secondary Diabetes Mellitus**

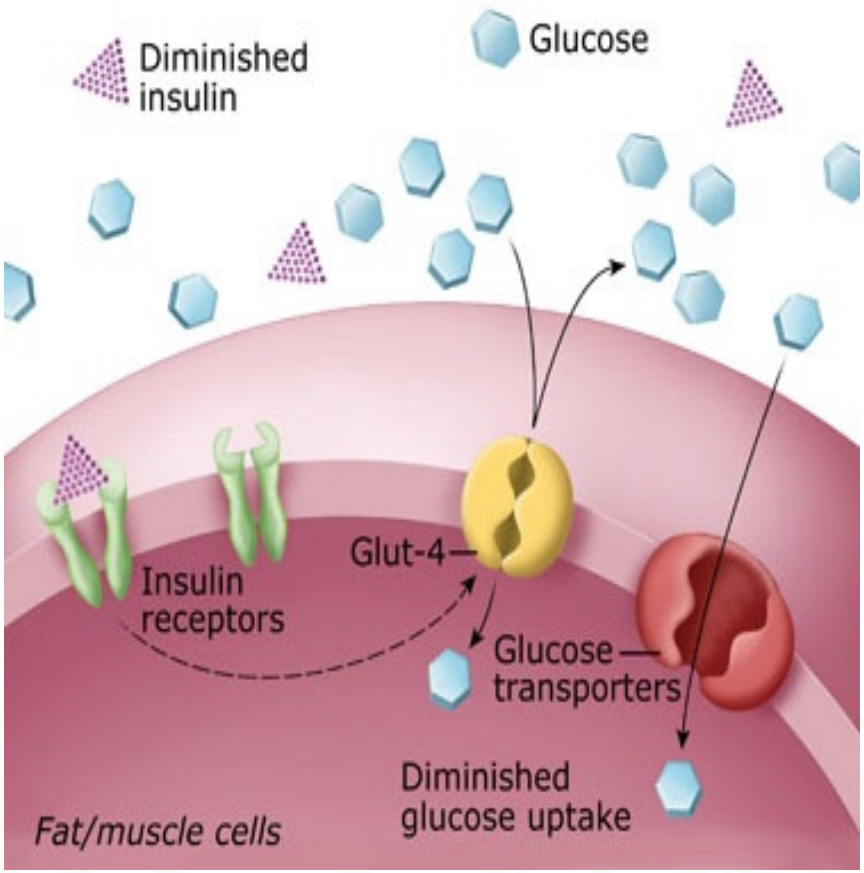
Type 1 diabetes

- Insulin-dependent diabetes mellitus (IDDM)
- Juvenile-onset diabetes.
- Immune system destroys pancreatic beta cells
- Children and young adults
- Although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.

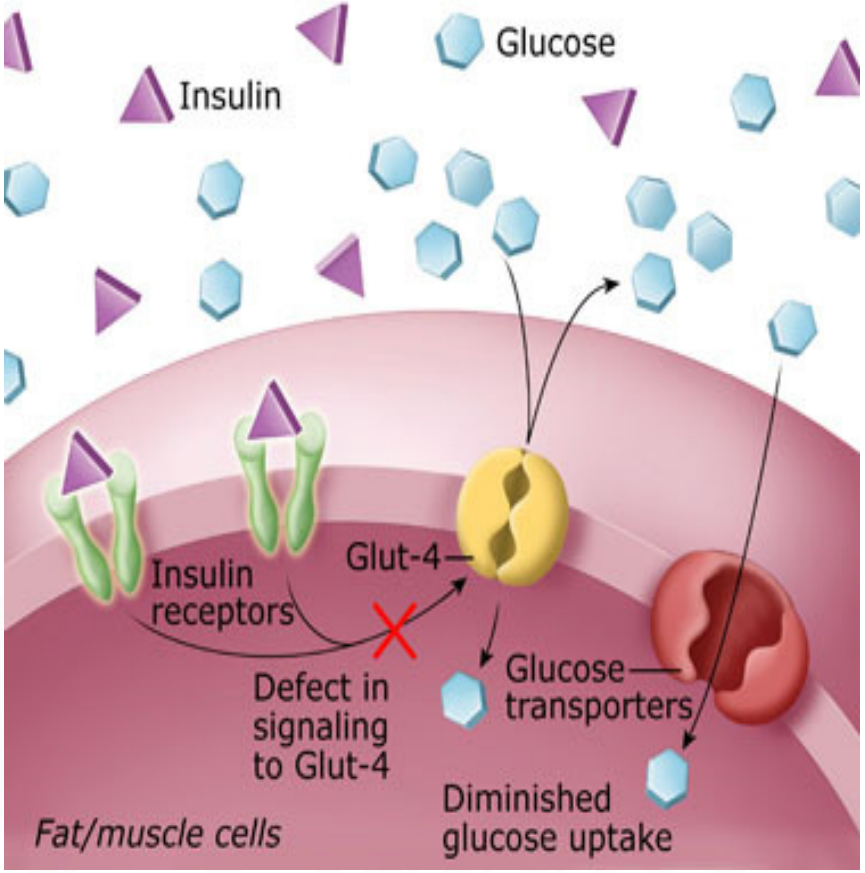
Type 2 diabetes

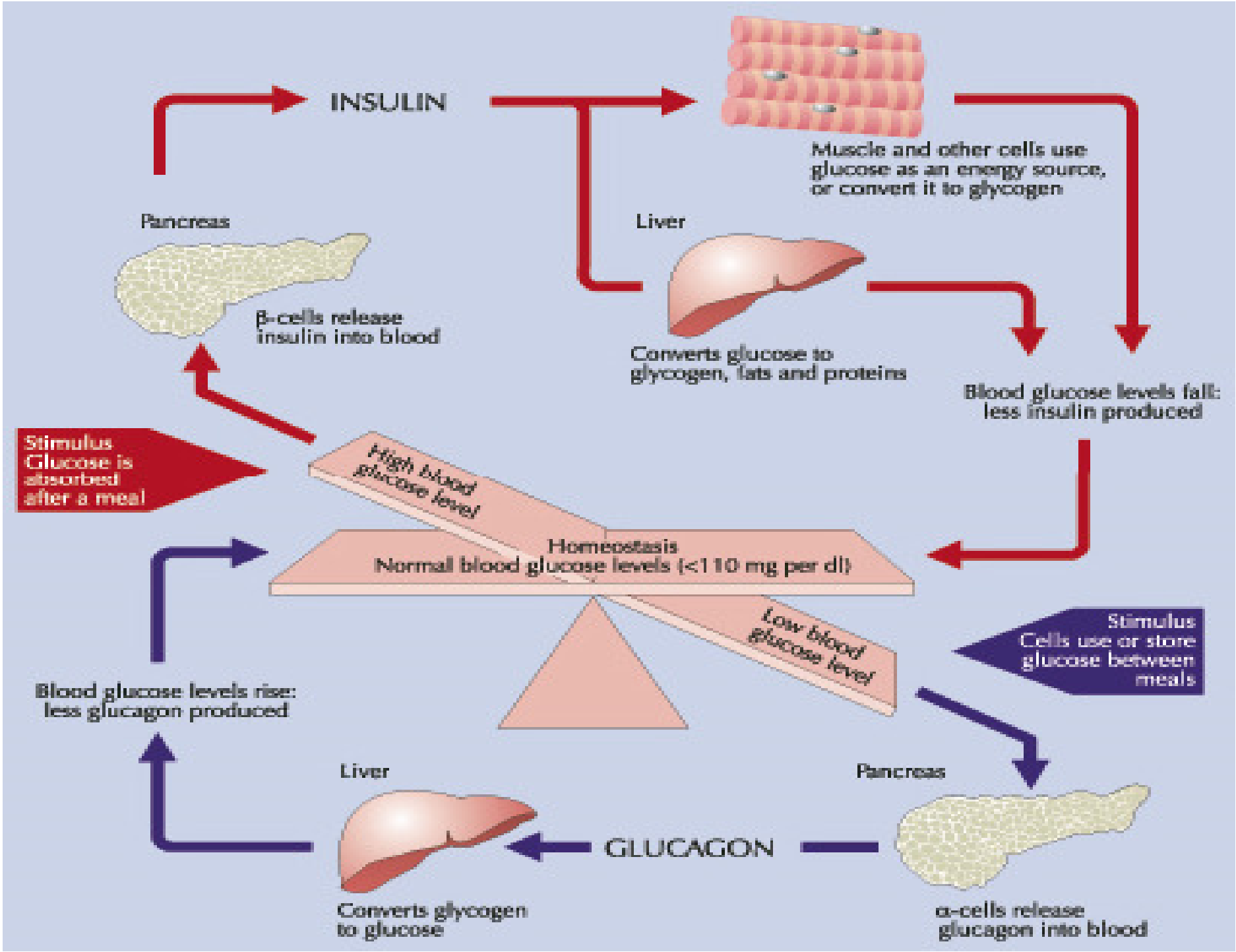
- Non-insulin-dependent diabetes mellitus (NIDDM)
- Adult-onset diabetes.
- 90% to 95% of all diagnosed cases of diabetes.
- Insulin resistance
- As the need for insulin rises
- & Pancreas gradually loses its ability to produce insulin.
- Associated with
  - Older age
  - Obesity & Physical inactivity
  - Family history of diabetes & History of gestational diabetes
  - Impaired glucose metabolism

Type 1 Diabetes: Insufficient Insulin



Type 2 Diabetes: Insulin Resistance




INSULIN
Muscle and other cells use glucose as an energy source, or convert it to glycogen
Pancreas
β-cells release insulin into blood
Liver
Converts glucose to glycogen, fats and proteins
Blood glucose levels fall: less insulin produced
Stimulus Glucose is absorbed after a meal
High blood glucose level
Homeostasis
Normal blood glucose levels (<110 mg per dl)
Low blood glucose level
Stimulus Cells use or store glucose between meals
Blood glucose levels rise: less glucagon produced
Liver
Converts glycogen to glucose
GLUCAGON
Pancreas
α-cells release glucagon into blood

Gestational diabetes

- **Diagnosed in some women during pregnancy.**
- **After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes.**

Other types of DM

- **Maturity Onset Diabetes of Young**
  - **Surgery**
  - **Drugs**
  - **Malnutrition**
  - **Infections**
  - **Other illnesses.**
- **1% to 5% of all diagnosed cases of diabetes.**

LADA

- Latent Autoimmune Diabetes in Adults (LADA)
- ***Autoimmune type 1 diabetes* at older age**
- "Slow Onset Type 1" diabetes

MODY

- MODY – Maturity Onset Diabetes of the Young
- Mutations
  - In enzyme glucokinase
  - In Receptor
- In sufficient insulin release from pancreatic ß-cells

Secondary DM

Secondary causes of Diabetes mellitus include:

- Acromegaly
- Cushing syndrome
- Thyrotoxicosis
- Pheochromocytoma
- Chronic pancreatitis
- Cancer
- Drug induced hyperglycemia

Reference Ranges

	FBS in mg%	PP2BS in mg %	HbA1C in %
Normal	70 – 110	< 140	4 – 6.5
Pre-Diabetic (Impaired Fasting Glycemia)	110 - 126	< 140	4 – 6.5
Pre-Diabetic (Impaired Glucose Tolerance)	110 - 126	140 – 200	6.5 – 7.0
Diabetes mellitus	> 126	> 200	> 7.0

Investigation

- FBS
- PP2BS
- Oral Glucose Tolerance Test
- I.V. Glucose Tolerance Test
- HbA1C
- Urinary Sugar - Protein
- Lipid Profile
- Renal Function Test
- Fundus Examination
  Nerve Conduction Study

Complications

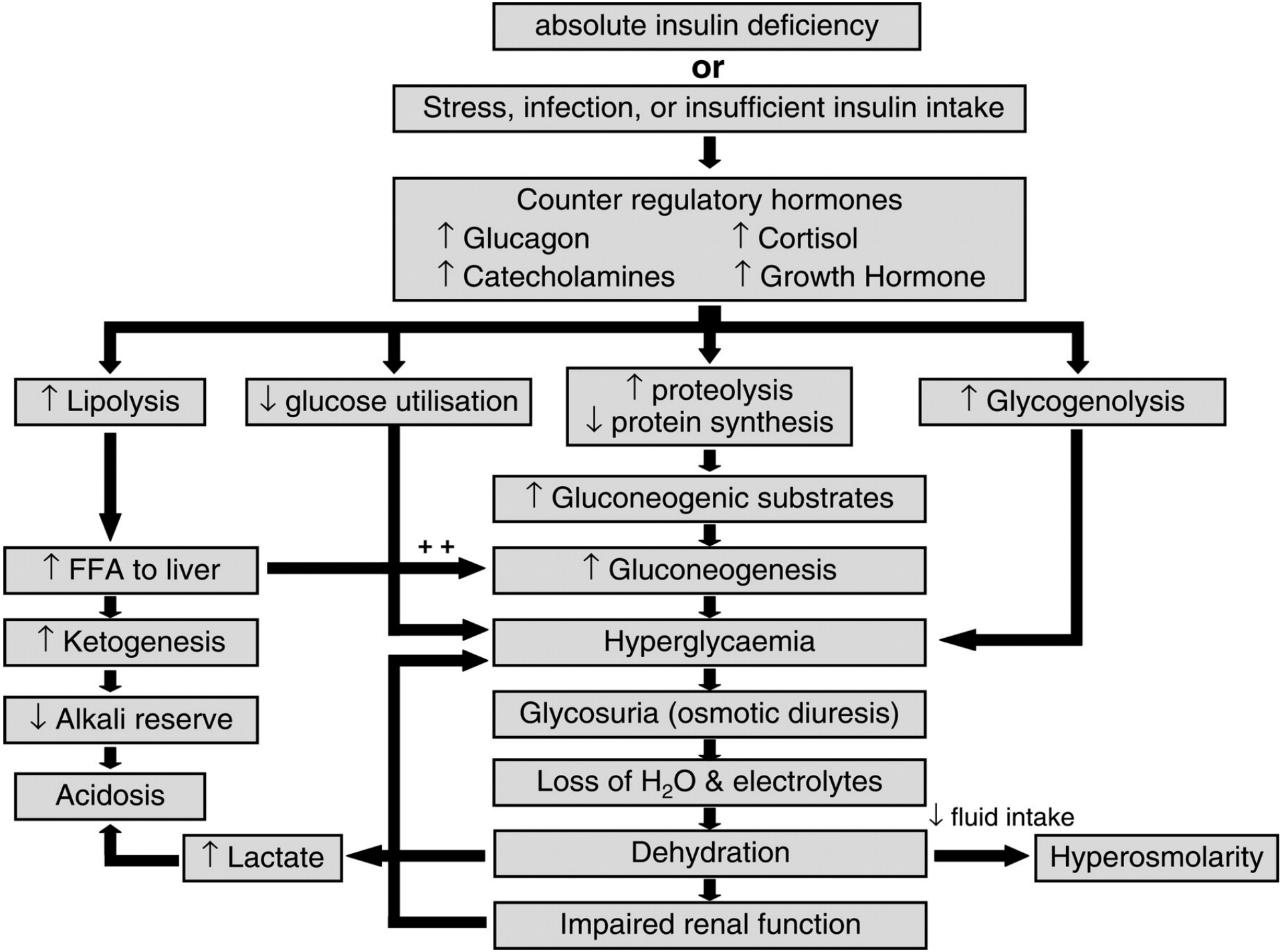
- Acute complications
- Chronic complications

Acute complications

- Diabetic Ketoacidosis
- Hyperosmolar Non-ketosis Coma
- Hypoglycemia

Diabetic ketoacidosis (DKA)

- Acute and dangerous
- On presentation at hospital,
  - Dehydrated
  - Hypotension & shock.
  - Breathing = Rapid and Deep.
  - Kussmull's breathing
  - Fruity smell from breath
  - May progress to coma.


absolute insulin deficiency
or
Stress, infection, or insufficient insulin intake
Counter regulatory hormones
↑ Glucagon
↑ Cortisol
↑ Catecholamines
↑ Growth Hormone
↑ Lipolysis
↓ glucose utilisation
↑ proteolysis
↓ protein synthesis
↑ Glycogenolysis
↑ Gluconeogenic substrates
↑ FFA to liver
+ +
↑ Gluconeogenesis
↑ Ketogenesis
Hyperglycaemia
↓ Alkali reserve
Glycosuria (osmotic diuresis)
Acidosis
Loss of H_2O & electrolytes
↓ fluid intake
↑ Lactate
Dehydration
Hyperosmolarity
Impaired renal function

Investigation in DKA

- Electrolyte
- Blood Glucose
- Blood Ketone body
- ABG
  - pH
  - pO_2
  - pCO_2
  - HCO_3^-

Hyperosmolar Nonketotic Coma

- Symptoms are similar to DKA
- Due to osmotic effect of high glucose levels
- water loss increases and eventually lead to dehydration.
- Progressively dehydrated
- Electrolyte imbalance.
- Lethargy
- Ultimately progress to a coma

Hypoglycemia

- Due to several diabetes treatments.
- Sweaty & Weak.
- Altered Consciousness
- Coma, Seizures
- **Caused by**
  - Too much dose of insulin or oral hypoglycemic drugs.
  - Incorrectly timed insulin
  - Too much or incorrectly timed exercise
  - Not enough food

Chronic complications

- Microvascular diseases
- Macrovascular diseases
  - Coronary artery disease
  - Peripheral vascular disease
  - Intermittent claudication
  - Stroke
  - Diabetic foot
- Most Common Pathogenesis for Chronic complication in DM , is AGE

Microvascular diseases

- Diabetic cardiomyopathy,
- Diabetic nephropathy
- Diabetic neuropathy
- Diabetic retinopathy

Advance Glycate End-Products

- It is “Non-Enzymatic Glycation of Protein or Lipid”
  - Protein /Lipid attached with Glucose , without Enzyme
  - This is called “Glycation” or “AGEs”
- Because of Protein Glycation
  - Protein structure get change
  - Protein denaturation
  - Protein function get affected because of protein glycation

Advance Glycate End-Products in Diabetes Mellitus

- Artery – Vessels – capillary
  - Arteriosclerosis , Atherosclerosis
- Eye lens
  - Cataract
- Glomerulus membrane
  - Nephropathy
  - CRF
- Nerves – Motor nerve , Sensory Nerve , Optic nerve
  - Motor & Sensory Neuropathy
  - Optic neuropathy
- Plasma protein – Haemoglobin, Albumin
  - HbA1C

Advance Glycate End-Products

- Glycate Haemoglobin – HbA1c
  - Life of HbA1c = 3 – 4 months = Life of RBC
  - Significant
    - Prognosis of DM patient
    - Chance of complication of DM
    - Glycation control of last 3 months

Management of Diabetes Mellitus

Management of DM

- The major components of the treatment of diabetes are:

A	• **Diet and Exercise**
B	• **Oral hypoglycaemic therapy**
C	• **Insulin Therapy**

Diet & Exercise

- **Dietary treatment should aim at:**
  - Ensuring weight control
  - Providing nutritional requirements
  - Allowing good glycemic control
  - Correcting any associated blood lipid abnormalities
- **Exercise**
  - Reduce abdominal obesity
  - Minimum 30 – 40 minutes brisk walking
  - Aerobic exercise

Nutritional Requirement

- Carbohydrate
  - 60-70% calories from carbohydrates & monounsaturated fats
- Protein
  - 10-20% total calories
- Fat
  - <10% calories from saturated fat
  - 10% calories from PUFA
  - <300 mg cholesterol
- Fiber
  - 20-35 grams/day
- Alcohol
  - Type I – limit to 2 drinks/day, with meals
  - Type II – substitute for fat calories

B. Oral Anti-Diabetic Agents

- Classes of Oral anti-diabetic agents:
  1. Sulfonylureas
  2. Biguanides
  3. Thiazolidinediones
  4. Alpha-glycosidase inhibitors
  5. Meglitinides
  6. Dipeptidyl peptidase-4 inhibitor

Sulfonylureas

Mechanism : Stimulation of insulin secretion

1st generation:

Tolbutamide

Chlorpropamide

2nd generation:

Glybenclamide

Glipizide

3rd generation:

Glymepiride

Biguanides

- Phenformin
- Metformin
- Mechanism
  - Decrease glucose production from Liver by mild inhibiting ETC complex –I
  - Decrease intestinal absorption of Glucose

Thiazolidinediones (TZDs)

- Representative Drugs

  Rosiglitazone

  Pioglitazone

- Pharmacological effects
  - Improving function of insulin sensitivity
  - Decrease insulin resistance

α-glucosidase inhibitors

- **Representative Drugs**
  - **Acarbose**
  - **Voglibose**
- **Mechanism**
  - **Competitively inhibiting alpha amylase**
  - **To inhibit digestion of starch & disaccharides**

- **Main adverse reaction**
  - **Flatulence, diarrhea.**

Meglitinides

- **Representative Drugs**

  Repaglinide

- **Key point**
  - Increase insulin release by inhibiting ATP-sensitive K^+-channel
  - No direct effect on insulin release
  - Used alone or together with biguanides
  - Carefully used for patients with kidney or liver impaired.

Dipeptidyl Peptidase-4 (DPP) Inhibitor

- Sitagliptin
- Saxaliptin

- Mechanism of Action
  - DPP-4 inactivate Incretins
  - So DPP-4 inhibitor increase incretins
  - Inhibit insulin degradation
  - Decrease Glucagon

Indication of Insulin Therapy

Short-term use:

- Acute illness, surgery, stress and emergencies
- Pregnancy
- Insulin may be used as initial therapy in type 2 diabetes
- in marked hyperglycaemia
- Diabetic ketoacidosis
- Hyperosmolar nonketotic coma

Long-term use:

- If targets have not been reached after optimal dose of combination therapyapy

Types of insulin

Insulin type/action (appearance)	Brand names (generic name in brackets)	Basal/bolus	Dosing schedule
Rapid-acting analogue (clear) Onset: 10–15 minutes Peak: 60–90 minutes Duration: 4–5 hours	Humalog® (insulin lispro) NovoRapid® (insulin aspart)	Bolus	Usually taken right before eating or to lower high blood glucose
Short-acting (clear) Onset: 0.5–1 hour Peak: 2–4 hours Duration: 5–8 hours	Humulin®-R Novolin®ge Toronto	Bolus	Taken about 30 minutes before eating, or to lower high blood glucose
Intermediate-acting (cloudy) Onset: 1–3 hours Peak: 5–8 hours Duration: up to 18 hours	Humulin®-N Novolin®ge NPH	Basal	Often taken at bedtime, or twice a day (morning and bedtime)
Extended long-acting analogue (Clear and colourless) Onset: 90 minutes Peak: none Duration: 24 hours	Lantus® (insulin glargine) Levemir® (insulin detemir)	Basal	Usually taken once or twice a day
Premixed (cloudy) A single vial contains a fixed ratio of insulins (the numbers refer to the ratio of rapid- or fast-acting to intermediate-acting insulin in the vial)	Humalog® Mix 25™ Humulin® (20/80, 30/70) Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50)	Combination of basal and bolus insulins	Depends on the combination

Treatment of DKA

1. Improve circulatory volume
2. Decrease Serum glucose
3. Clear serum of ketonebodys
4. Correct electrolyte imbalances

Treatment of DKA

Principles of Treatment:

- Replacement of fluid deficits.
- Correction of acidosis & hyperglycemia via Insulin administration.
- Correction of electrolytes imbalance.
- Treatment of underlying cause.

Fluids replacement

Intravenous solutions

- Replace extravascular and intravascular fluids
- Replace electrolyte losses
- Dilute both the glucose level

Insulin is needed to help

- switch from a catabolic state to an anabolic state
- uptake of glucose in tissues
- reduction of gluconeogenesis
- reduce ketone production.

Fluid Correction

- Initial correction of fluid loss is either
  - by isotonic NaCl solution
  - by lactated Ringer solution.
- The recommended schedule :
  - Administer 1 -3 L during the first hour.
  - Administer 1 L during the second hour.
  - Administer 1 L during the following 2 hours
  - Administer 1 L every 4 hours
- When blood sugar < 180 mg/dL
  - 5-10% dextrose with half isotonic NaCl solution.
- In maintainance, half-normal saline at 200-1000 mL/h

Insulin Therapy

- **Regular insulin infusion = 0.1 U/kg/hour**
- **Serum Glucose should not decrease more than**
- **100mg%/hour**
- **If Glucose falls < 200 prior to correction of acidosis,**
  - **change IV fluid from 5% Dextrose or 10 % dextrose**
  - **But don't decrease the rate of insulin infusion.**
- **Use initial bolus of insulin (IV/IM) is controversial.**

Correction of Acidosis

- **Insulin therapy**
  - **Stops Lipolysis**
  - **Decrease production of ketone bodies.**
- **Normal saline**
  - **Correction of dehydration**
  - **Normalize the blood PH.**
- **Bicarbonate therapy**
  - **should not be used unless severe acidosis (pH<7.0)**

Correction of Electrolyte Imbalance

- **If K+ is low.**
  - **As soon as the urine output is restored, potassium supplementation**
- **If K+ is hiigh**
  - **Potassium should be corrected**
    - **Furosemide**
    - **Insulin**
    - **Salbutamol**
    - **Bicorbonate**

Thank You