Diabetes Mellitus (DM)

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Magnitude of the problem

- DM is one of the most common metabolic diseases of human beings.
- About 135 million people worldwide are affected with the most common form, type 2.
- Is the 6th leading cause of death in USA
- In Eastern Mediterranean Region, it is now the 4th leading cause of death

Identification

- It is a **chronic** disease due to:
  - **Absolute deficiency or**
  - **Diminished effectiveness of insulin**

- The disease **affects the metabolism of carbohydrates, proteins, fats, water and electrolytes.**

Classification

I. **Diabetes mellitus**

II. **Impaired glucose tolerance**

III. **Gestational DM**

I. Diabetes Mellitus

- **Insulin dependant DM**
  - **(Juvenile onset, IDDM, type I)**
- **Non insulin dependant DM**
  - **(Maturity onset, NIDDM, type II)**
- **Malnutrition related DM**
- **Drug or hormonal induced DM.**

II. Impaired glucose tolerance

Intermediate state between DM and normality:

- **May be precipitated by:**
  - **Pregnancy**
  - **Obesity and**
  - **Stress**

III. Gestational DM

- **Pregnancy-induced**

Type I (IDDM)

- Is the **most** lethal form, having an **abrupt** onset.
- Associated with an **absolute** and complete insulin **deficiency**, due to destruction of β-cells of the pancreas by viruses and autoantibodies.
- Usually occur in **young** patient during childhood and puberty.
- Patient requires **Insulin** therapy in addition to diet control.

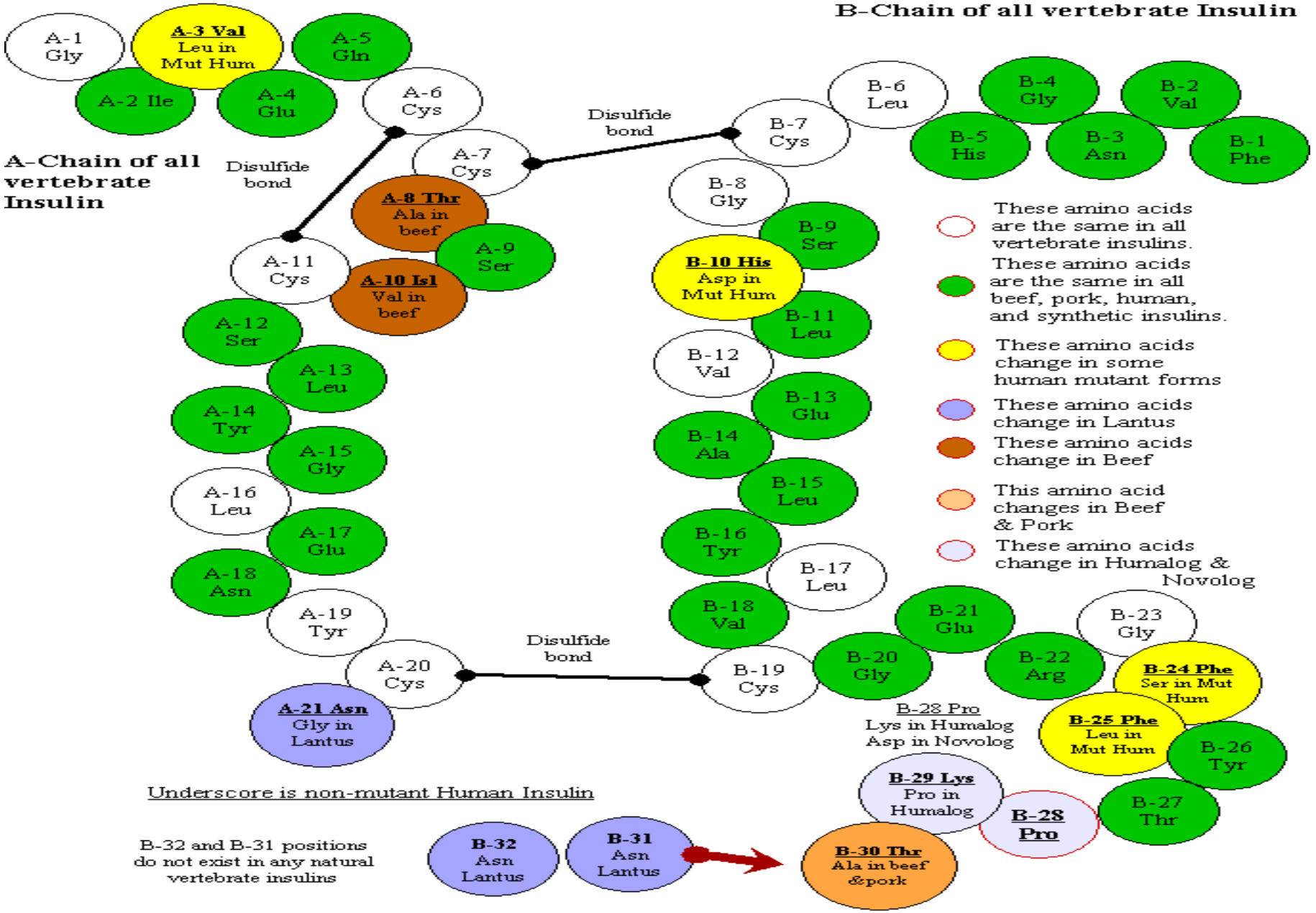
Type II (NIDDM)

- Is the **commonest** presentation, with **gradual** onset.
- Associated with a **relative** insulin deficiency, the pancreas can secrete insulin, but there is insulin **resistance**.
- Usually occurs in **overweight** patient **over** the age of **35** years and **genetic** factor play an important role.
- Patient require **weight reduction**, **diet** control and oral hypoglycaemic **drugs**. Insulin may also required.

Drugs therapy of DM

- Anti-Diabetic medications
  - **Insulin**
  - **Oral hypoglycemic agents**

Insulin

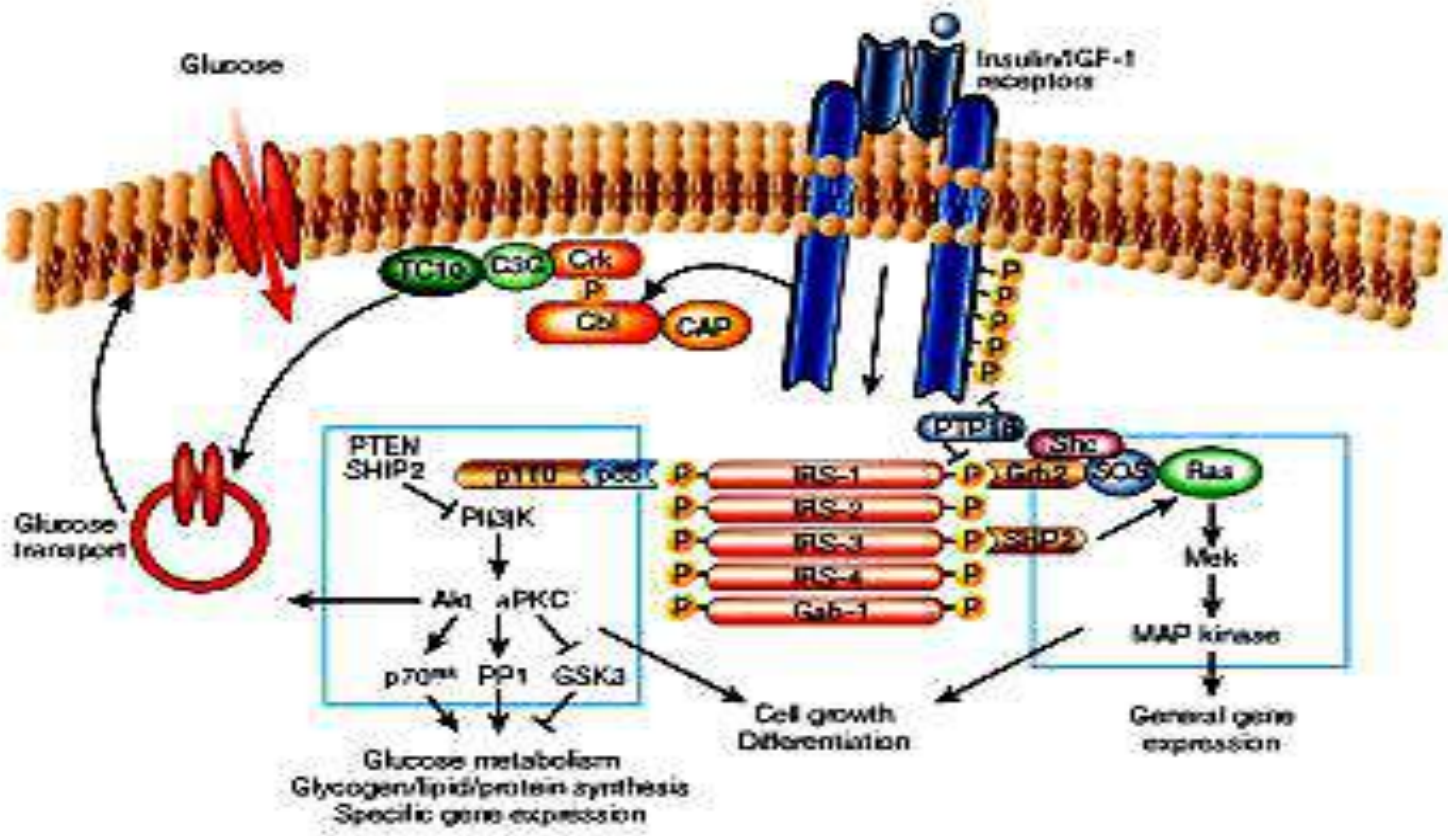


The Insulin Molecule for all vertebrates and synthetic insulins as of 11/2002.

Insulin

- **Daily** secretion of insulin is about **30-40 units**.
- Synthesized, stored and secreted by the **β-cells** of the pancreas.
- Blood **glucose** levels and other factors (other sugars, aa, vagus activity) control insulin secretion.
- Is removed from circulation by the liver and kidneys.

Mechanisms of Insulin Action



Saltiel and Kahn, Nature 414, 799-806, 2001

Insulin binds to specific receptors on cell membrane ⟶ Insulin-receptor complex enters cells ⟶ Auto-phosphorylation ⟶ Production of insulin actions

Insulin actions

- **Increase glucose transport** into **tissues**
- **Increase glucose utilization** by **tissues:**
  - Increase glycogen and fat synthesis
- **Decrease hepatic output** of **glucose**
  - Decrease glycogenolysis and gluconeogenesis

  All these actions lead to:
- **Reduction** of **blood glucose**
- **Stimulation** of **appetite**
- **Enhancement** of **protein** synthesis
- **Inhibition** of **lipolysis**

Insulin

In diabetics, these actions will **correct:**

- **Symptoms** of diabetes like:
- ✓ **Glycosuria**
- ✓ **Polyuria and**
- ✓ **Polydypsia**

Excessive insulin secretion

Occurs in:

- **Presence of insulin resistance**
  - Diminished ability of cells to respond to actions of insulin in transporting glucose from bloodstream into muscle and other tissues

- **Overeating**

Diet control and exercise

Will:

Reduce overeating

↓

Reduce excessive insulin secretion

↓

Increase insulin receptors number (up-regulation)

↓

Restore insulin sensitivity

Uses of insulin

- **Control of DM** in**:**
  - **All** patient with **IDDM** and
  - **Some** with **NIDDM (**uncontrolled)
- **Hyperkalaemia**:
  - insulin enhances potassium entry into cell with glucose.
- **Insulin hypoglycaemia test:**
  - To study anterior pituitary function (GH and ACTH release)

Insulin Pharmacokinetic

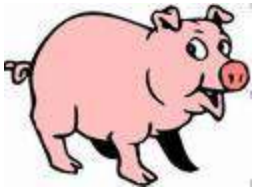
- Given **parenterally** (IV, IM or SC injection)
  - Never orally (destroyed by gastric pH)
- **Metabolized** by **insulinase** in liver and kidneys about 10% appear in the urine.
- t½ is 5 min.
- **New techniques** of **administration:**
  - Insulin pens
  - External infusion and implantable pumps and
  - Sustained-release preparations.

Insulin Adverse Effects

- **Hypoglycaemia** commonest reaction to an overdoses of insulin. It may lead to:
  - Tachycardia, tremor, sweating and hunger
  - Convulsions, coma and death
  - Disturbed sleep and morning headache
- **Lipodysthrophy** at injection sites
  - atrophy or hypertrophy of sc fatty tissues
- **Allergic** reaction (uncommon, may be due to the Zn component of insulin)

Insulin preparations origin

Insulin differs by 3 aa from human insulin



Insulin differs by 1 aa from human insulin

Are antigenic

Recombinant DNA technology

Less immunogenic, absorbed faster than animal insulin and has shorter duration of action

Insulin Preparations

- **Rapid** action insulin:
  - Is soluble form
  - Only form given **IV, IM or SC**
  - Acts within **30** min with **3-5**hr duration of action
  - Useful in controlling DM, diabetic ketoacidosis and after surgery.
- **Very rapid** action:
  - Is **new** modified recombinant **human** insulin
  - Acts within **15 min** with **2-5**hr duration of action

Insulin Preparations

- **Intermediate** action insulins:
  - Combined & suspended with protamine or Zn,
  - Given SC **twice** daily

- **Long** action insulin: (Zn suspension and protamine Zn insulin
  - Given SC **once** daily

Oral Hypoglycaemic Agents

Increase Insulin Release

- **Sulfonylureas**
- **Meglitinides**

Improve Insulin Action

- **Biguanides**
- **Thiazolidinediones (TZDs)**

Reduce Dietary Intake

- **α-glucosidase inhibitors**

Useful to treat **NIDDM** not responding to diet control alone.

Increase Insulin Release

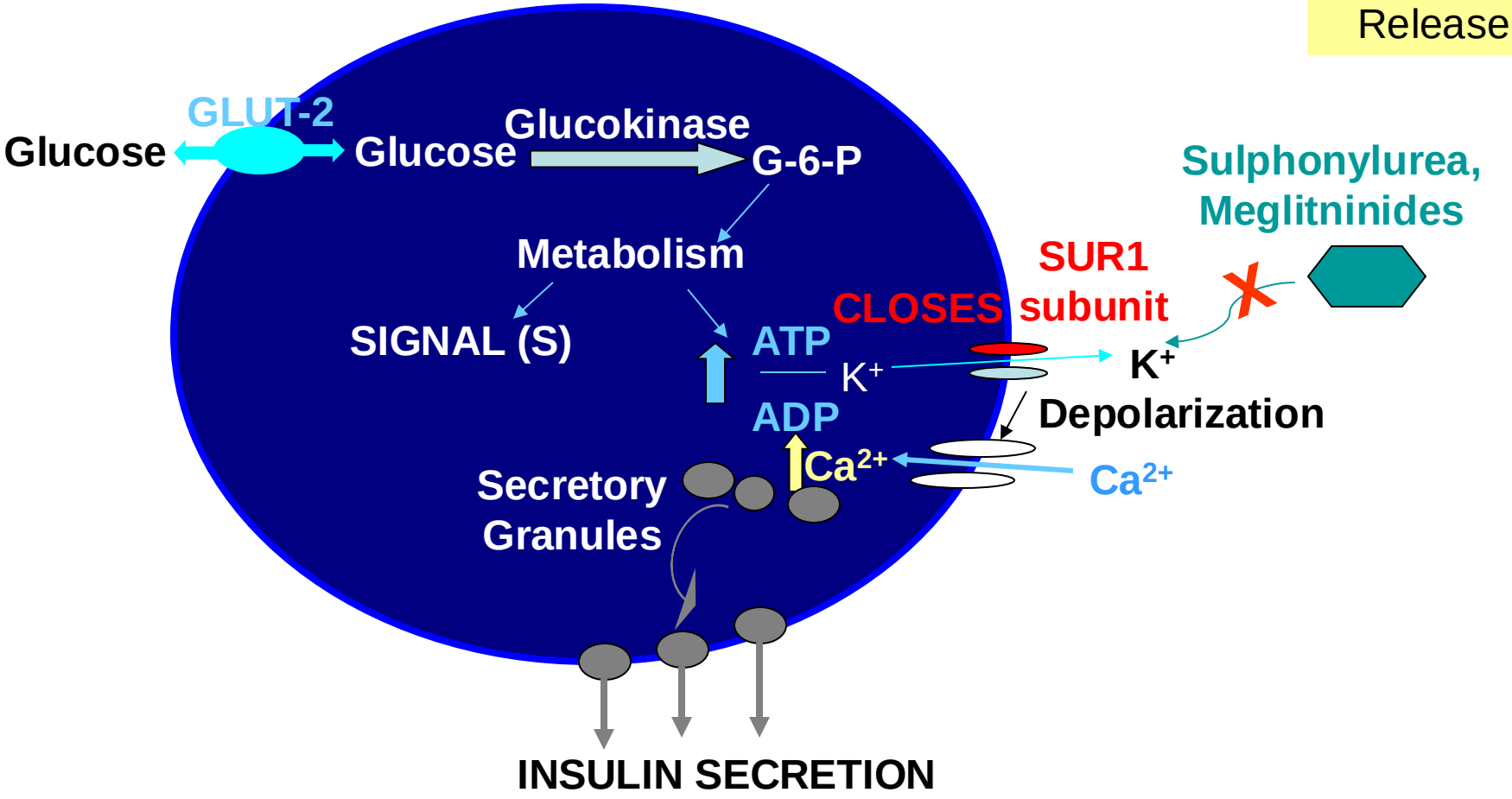
Sulphonylurea drugs

- **1st** generation drugs:
  - Tolbutamide, **glibenclamide**, chlorpropamide
- **2nd** generation drugs:
  - Gliclazide & glipizide more potent (16-24 Hr)
- Act by:
  - **Increase insulin release**
  - **Reduce glucagon** release (glucogenolysis)

  These result in:
  - **Decreased** hepatic **glucose output** and
  - **Increased glucose uptake** in the muscle.
- Successful therapy **requires functioning β-cells** (~30%)

Sulphonylureas mechanism of action

Increase Insulin Release



Sulfonylureas bind to an ATP-dependent K^+ (KATP) channel on the cell membrane of pancreatic β-cells. This inhibits a tonic, hyperpolarizing outflux of K^+, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular Ca^{2+} leads to increased fusion of insulin granules with the cell membrane, and therefore increased secretion of (pro)insulin.

Increase Insulin Release

Sulphonylurea Pharmacokinetic

- Highly **protein bound**
- **Metabolized** in the **liver** and **excreted** by the **liver and kidneys**
- **Caution** in ptes with advanced **renal or hepatic impairment**
- **Avoid** used during **pregnancy**
  - **Insulin** should be used during **pregnancy**

Increase Insulin Release

Sulphonylurea adverse effects

- **Long** acting agent (glibenclamide and chlorpropamide) have higher risk to **hypoglycaemia** than shorter agent (tolbutamide and gliclazide), therefore **avoided** in **elderly.**
- Cause **weight gain**
- Disulfiram-like **reaction** with **alcohol** (nausea, **flushing**, hypotension)

Increase Insulin Release

MEGLITINIDES (**Repaglinide** and nateglinide)

- Same mechanism **as sulfonylureas**, different binding sites
  - Meglitinides: manage mealtime glucose rise (Controls postprandial hyperglycaemia)
  - Similar efficacy to sulphonylurea
- **Rapid** onset, **short** duration (1-2 hrs)
- **Less hypoglycemia** due to more rapid kinetics

Successful therapy **requires functioning β-cells**

Improve Insulin Action

Biguanides (Metformin)

- Primary action at liver:
  - **Reducing** hepatic glucose **synthesis**
  - Increases glucose **uptake**
  - **Slowing** of glucose **absorption** from GIT
  - Increase insulin receptor sensitivity
- **Hypolipidemic** effect
  - reduction of cholesterol, VLDL, LDL and increase HDL
- Promotes modest **weight loss** (1st line in overweight DM ptes)
- Metformin given **alone** or in **combination** with a **sulfonylurea**
- Is **not protein bound**, is **excreted unchanged** in urine
- **Decreased** cardiovascular **risk** and **complication** of diabetes

Effective only in the presence of insulin

Metformin mechanism of action

Improve Insulin Action

Biguanides (Metformin) ***adverse effects***

- **Lactic acidosis** due to impairment of hepatic metabolism of lactic acid.
- **GI upset**: Nausea, cramping, and diarrhea (can minimized taking with meals and starting at low dose)
- Is **contraindicated in renal and hepatic** disease
- Does **not** cause **hypoglycaemia**

Improve Insulin Action

Thiazolidinediones (TZDs) (**Rosiglitazone** and Pioglitazone)

- Primary action in periphery:
  - **Reduces lipolysis, increases muscle uptake**
- Secondary action at liver:
  - **Reduces hepatic glucose production**

TZDs **reduce** peripheral **insulin resistance** and reduce **blood glucose** by:

- **Insulin-mimetic** activity

Thiazolidinediones Adverse effects

- Mild **Anaemia**
- **Weight gain**
- **Hypoglycaemia** may occur if used in combination with other hypoglycaemic drugs
- **Fluid retention** may occur in ptes with heart failure, for this reason **avoid** in ptes with moderate or severe **angina** or **heart failure**.

Reduce Dietary Intake

α-glucosidase inhibitors (Acarbose)

- Often **used** in **combination** with other hypoglycaemic oral drugs in NIDDM ptes and with insulin in IDDM ptes.

Mechanism of action

- **Inhibit pancreatic α-glucoside enzyme** in the intestine
- Modulate GI absorption and digestion of carbohydrates (**delays the carbs absorption)**

Advantages

- **Decreases HbA_{1c}** (glycosylated hemoglobine) by 0.5-1.0%
- Control postprandial hyperglycaemia

Adverse effect

- **GI disturbance** (bloating, flatulence, diarrhoea and abdominal pain)