DRUGS FOR DIABETES

The pancreas produces the peptide hormones insulin (from β cells), glucagon (fromα cells), and somatostatin (from δ cells). These hormones play an essential role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycaemia. If untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. However, administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes.

DIABETES MELLITUS

- **Diabetes** is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin.
- The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes (formerly insulin- dependent diabetes mellitus), type 2 diabetes (formerly non– insulin-dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes such as genetic defects or medications.
- Gestational diabetes (GD) is defined as carbohydrate intolerance with onset or first recognition during pregnancy. Uncontrolled GD can lead to fetal macrosomia (abnormally large body) and difficult delivery, as well as neonatal hypoglycemia. Diet, exercise, and/or insulin administration are effective in this condition. In addition, glyburide and metformin may be reasonable alternatives to insulin therapy for GD.

Type 1 diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune-mediated processes (that may be triggered by viruses or other environmental toxins) usually leading to absolute insulin deficiency and appearance of classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss). Eventually, all type1 diabetic patients will require insulin therapy to maintain normglycemia.

Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes.

- **Cause:** Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin. In type 2 diabetes, the pancreas retains some β-cell function, but insulin secretion is insufficient to maintain glucose homeostasis in the face of increasing peripheral insulin resistance.
- **The goal** in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications.
- Healthy life style can help to get this goal; however, most of the patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and insulin therapy is often needed to achieve satisfactory glucose levels.

The blood glucose level can be monitored using different tests and the most important ones are the measuring of **Plasma or Serum Glucose or the measurement of the glycosylated hemoglobin (HbA1c) as demonstrated in table 1.**

Table 1: Diagnostic criteria for diabetes.

	Normal Glucose Tolerance, mg/dL (mMol/L)	Prediabetes	Diabetes Mellitus[2]
Fasting plasma glucose mg/dL (mmol/L)	<100 (5.6)	100–125 (5.6–6.9) (impaired fasting glucose)	≥126 (7.0)
Two hours after glucose load[1] mg/dL (mmol/L)	<140 (7.8)	≥140–199 (7.8–11.0) (impaired glucose tolerance)	≥200 (11.1)
HbA_{1c} (%) (ADA criteria)	<5.7	5.7–6.4	≥6.5

[1]Give 75 g of glucose dissolved in 300 mL of water after an overnight fast in persons who have been receiving at least 150–200 g of carbohydrate daily for 3 days before the test.

[2]A fasting plasma glucose ≥126 mg/dL (7.0 mmol) or HbA_{1c} ≥ 6.5% is diagnostic of diabetes if confirmed by repeat testing.

Symptoms and random glucose level >200 mg/dL (11.1 mmol/L) are diagnostic, and there is no need to do additional testing.

MEDICATIONS FOR HYPERGLYCEMIA

1- INSULIN

Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β cells of the pancreas. Insulin secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K+ channels, leading to membrane depolarization and an influx of Ca^{2+} . The increase in intracellular Ca2+ causes pulsatile insulin exocytosis.

Mechanism of action

Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.

Pharmacokinetics and fate

- Human insulin is produced by recombinant DNA technology using strains of Escherichia coli or yeast that are genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties.
- Insulin preparations vary primarily in their onset and duration of activity. For example, insulin lispro has a faster onset and shorter duration of action than regular insulin, because it does not aggregate or form complexes.
- Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations.
- Because insulin is a polypeptide, it is degraded in the GIT if taken orally. Therefore, it is generally administered by subcutaneous injection and inhaled insulin formulation is also available. However, in a hyperglycemic emergency, regular insulin is administered intravenously (IV).

INSULIN PREPARATIONS AND TREATMENT

Insulin preparations are classified as rapid-, short-, intermediate-, or long-acting.

Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: regular insulin, insulin lispro, insulin aspart, and insulin glulisine.

- Regular insulin is a short-acting, soluble, crystalline zinc insulin while Insulin lispro, aspart, and glulisine are classified as rapid-acting insulins.
- Peak levels of rapid-acting insulins are seen at 30 to 90 minutes, as compared with 50 to 120 minutes for regular insulin.
- Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulin and to control postprandial glucose. They may also be used in cases where swift correction of elevated glucose is needed.
- Rapid- and short-acting insulins are usually used in conjunction with a longer-acting basal insulin that provides control of fasting glucose.
- Regular insulin should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered in the 15 minutes proceeding a meal or within 15 to 20 minutes after starting a meal.
- Both rapid-acting and regular insulin can be used when the IV route is needed.

Intermediate-acting insulin

- Neutral protamine Hagedorn (NPH) insulin (or insulin isophane) is an intermediate-acting insulin formed by the addition of zinc and protamine to regular insulin.
- The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action.
- NPH insulin is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control.
- NPH insulin should be given only subcutaneously (**never IV**), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).

Long-acting insulin preparations

- Insulin glargine can be precipitated at the injection site that leads to releasing insulin over an extended period.
- It has a slower onset than NPH insulin and a flat, prolonged hypoglycemic effect with no peak.
- Insulin detemir has affinity to bind with albumin and the slow dissociation from albumin resulting in long-acting properties similar to those of insulin glargine.
- As with NPH insulin, insulin glargine and insulin detemir are used for basal control and should only be administered subcutaneously.
- Neither long-acting insulin should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.

Insulin combinations

- Various premixed combinations of human insulins, such as 70% NPH insulin plus 30% regular insulin, or 50% of each of these are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

Insulin Delivery Systems

1- **Insulin Syringes and Needles:** Disposable plastic syringes with needles attached are available in 1-mL (100 units), 0.5-mL (50 units), and 0.3-mL (30 units) sizes.

2- **Insulin Pens**

The pens eliminate the need for carrying insulin vials and syringes. Cartridges of insulin lispro, insulin aspart, and insulin glargine are available for reusable pens.

3- **Continuous Subcutaneous Insulin Infusion Devices (CSII, Insulin Pumps)**

Continuous subcutaneous insulin infusion devices are external open-loop pumps for insulin delivery. The devices have a user programmable pump that delivers individualized basal and bolus insulin. Replacement doses based on blood glucose self-monitoring results.

4- **Inhaled Insulin:** A dry powder formulation of recombinant regular insulin is now approved for use in adults with diabetes.

Side effects of insulin therapy

1- Hypoglycemia is the major risk that must be weighed against benefits of efforts to normalize glucose control. The main signs and symptoms of hypoglycaemia are: Irregular heart rhythm, fatigue, pale skin, shakiness, anxiety, sweating, hunger, irritability. If untreated, hypoglycaemia worsens and can cause confusion, abnormal behaviour or both, such as the inability to complete routine tasks. Moreover, it can cause visual disturbances, such as blurred vision, seizures and finally loss of consciousness.

2- Other adverse effects include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.

2- ORAL AGENTS

- Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet. Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycaemia.
- Several categories of glucose-lowering agents are available for patients with type 2 diabetes, the main categories are:

A- Agents that bind to the sulfonylurea receptor and stimulate insulin secretion (sulfonylureas and glinides).

B- Agents that lower glucose levels by their actions on liver, muscle, and adipose tissue (biguanides, thiazolidinediones)

C- Agents that principally slow the intestinal absorption of glucose (α-glucosidase inhibitors).

A- Sulfonylureas (such as glyburide, glipizide, and glimepiride)

These agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas.

Mechanism of action: The main mechanism of action includes stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization, Ca2+ influx, and insulin exocytosis.

- In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

Adverse effects

- Adverse effects of the sulfonylureas include hypoglycemia, hyperinsulinemia, and weight gain. They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for glyburide, as it may increase the duration of action and increase the risk of hypoglycemia significantly. Glipizide or glimepiride are safer options in renal dysfunction and in elderly patients.
- Some **Drugs may reduce the effects of sulfonylureas, leading to loss of glucose control such as corticosteroids while others can potentiate the effects of sulfonylureas, leading to hypoglycaemia such as chloramphenicol and Clarithromycin.**

B- Glinides

This class of agents includes repaglinide and nateglinide. Glinides are also considered insulin secretagogues.

Mechanism of action:

- Like the sulfonylureas, the glinides stimulate insulin secretion. In contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators.
- Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.
- Glinides should be taken prior to a meal and are well absorbed after oral administration.

C- **Biguanides (**Metformin, the only biguanide, which is well absorbed orally.)

Is classified as an insulin sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Unlike sulfonylureas, metformin does not promote insulin secretion. Therefore, hyperinsulinemia is not a problem, and the risk of hypoglycemia is far less than that with sulfonylureas.

Mechanism of action:

- The main mechanism of action of metformin is reduction of hepatic gluconeogenesis. Also, it slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.
- Weight loss may occur because it causes loss of appetite.
- The ADA recommends metformin as the initial drug of choice for type 2 diabetes.
- Metformin may be used alone or in combination with other oral agents or insulin. However, hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

Adverse effects:

- These are largely gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea).
- Metformin should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse or patients who have renal dysfunction.
- Long-term use may interfere with vitamin B12 absorption.

Other uses: *metformin is effective in the treatment of polycystic ovary syndrome. It lowers insulin resistance seen in this disorder and can result in ovulation and, therefore, pregnancy.*

D- Thiazolidinediones (The 2 members of this class are *pioglitazone* and *rosiglitazone)*

The thiazolidinediones (TZDs) are also *insulin* sensitizers. Although *insulin* is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.

Mechanism of action

- The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator–activated receptor-γ (PPARγ). Activation of PPARγ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle
- The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin. The dose of insulin may have to be lowered when used in combination with these agents.
- The ADA recommends pioglitazone as a 2nd or 3rd line agent for type 2 diabetes.
- TZDs are well absorbed after oral administration and no dosage adjustment is required in renal impairment.

Adverse effects:

- Liver toxicity have been reported with these drugs, and periodic monitoring of liver function is recommended.
- Weight gain can occur because TZDs may increase subcutaneous fat and cause fluid retention that can worsen heart failure. So, These drugs should be avoided in patients with severe heart failure.
- TZDs have been associated with osteopenia and increased fracture risk in women.

E- α-Glucosidase inhibitors

Acarbose and *miglitol* are oral agents used for the treatment of type 2 diabetes.

Mechanism of action:

- Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed. *Acarbose* and *miglitol* reversibly inhibit α-glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels.
- Since they do not stimulate *insulin* release or increase *insulin* sensitivity, these agents do not cause hypoglycaemia when used as monotherapy. However, when used with *insulin* secretagogues or *insulin,* hypoglycaemia may develop.
- It is important that hypoglycaemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.
- *Acarbose* is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine.

Adverse effects:

- The major side effects are flatulence, diarrhoea, and abdominal cramping. Adverse effects limit the use of these agents in clinical practice.
- Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.