Drugs for Diabetes

Lecture 2

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Diabetes Mellitus

- Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to insulin deficiency or insulin resistance or both.
- The clinical classifications of diabetes is:

1. Type 1 diabetes (formerly insulin-dependent diabetes mellitus).
2. Type 2 diabetes (formerly non-insulin dependent diabetes mellitus).
3. Gestational diabetes.
4. Diabetes due to other causes (e.g., genetic defects, infection, or medication induced).

	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5% to 10% of diagnosed diabetics	90% to 95% of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

1. Type 1 diabetes

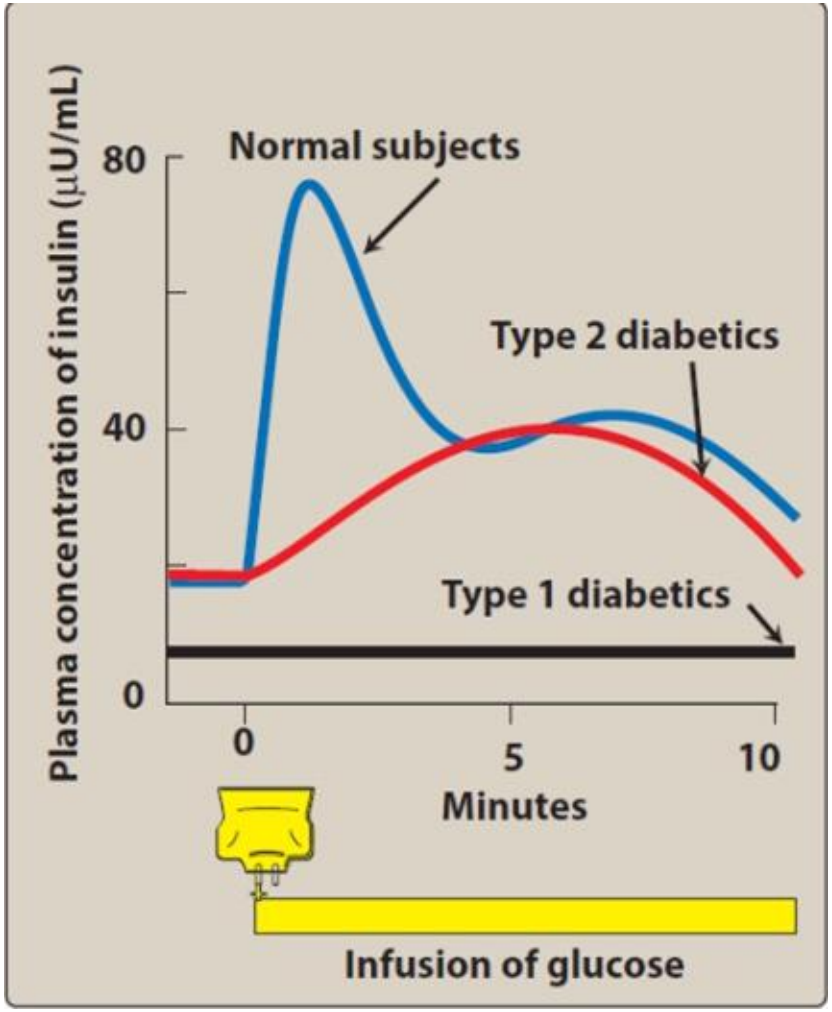
Cause: The disease is characterized by an absolute deficiency of *insulin* due to destruction of β cells. Loss of β-cell function results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins. As a result of the destruction of these cells, the pancreas fails to respond to glucose.

- In a normal postabsorptive period, constant β-cell secretion maintains low basal levels of circulating insulin. This suppresses lipolysis, proteolysis, and glycogenolysis.
- A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids. This lasts for up to 15 minutes, followed by the postprandial secretion of insulin.
- Type 1 diabetic shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss).
- Type 1 diabetics require exogenous insulin to avoid severe hyperglycemia and the life-threatening catabolic state of ketoacidosis.

2. Type 2 diabetes

- Most diabetics are Type 2. The disease is influenced by *genetic factors, aging, obesity, and peripheral insulin resistance* rather than by autoimmune processes or viruses.

- The metabolic alterations observed are milder than those described for Type 1 (for example, Type 2 patients typically are not ketotic), but the long-term clinical consequences are similar.



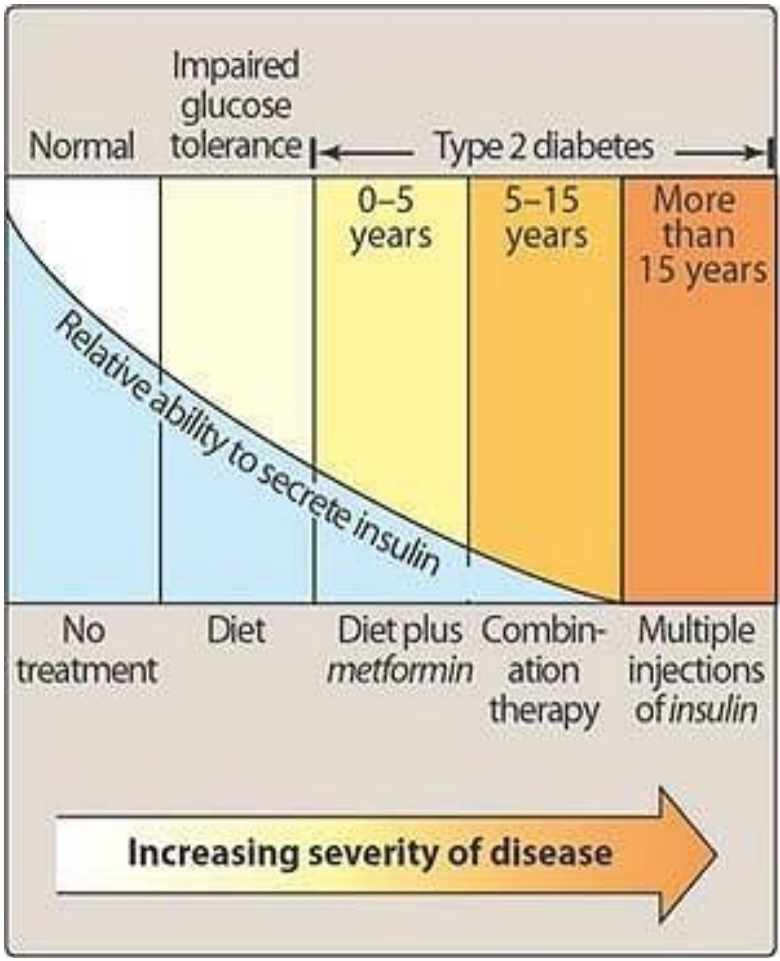
Treatment of Type-2 Diabetes

- The goal in treating Type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease.

- *Weight reduction, exercise, and dietary modification* decrease insulin resistance and correct the hyperglycemia of Type 2 diabetes in some patients.

- However, most patients require pharmacologic intervention with **Oral hypoglycemic agents**.

- As the disease progresses, B-cell function declines, and insulin therapy is often required to achieve satisfactory serum glucose levels



I- Insulin and insulin analogs

- 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.
- [Note: Because *insulin* undergoes significant hepatic and renal extraction, plasma *insulin* levels may not accurately reflect *insulin* production. Thus, measurement of C-peptide provides a better index of *insulin* levels.]
- 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 Ca2+. The increase in intracellular Ca2+ causes pulsatile insulin exocytosis.

-continue- Insulin and insulin analogs

- Human insulin is produced by *recombinant DNA technology* using special strains of *Escherichia coli* or yeast that have been genetically altered to contain the gene for human insulin.

- Modifications of the amino acid sequence of human insulin have produced insulin with different pharmacokinetic properties. For example:

1. *Lispro, Aspart, and Glulisine* - have a faster onset and shorter duration of action than regular insulin, because they do not aggregate or form complexes.
2. Glargine and Detemir are long-acting insulins and show prolonged, flat levels of the hormone following injection.

II- Insulin administration

- It therefore is generally administered by subcutaneous injection.

- In a hyperglycemic emergency, regular insulin is injected intravenously.

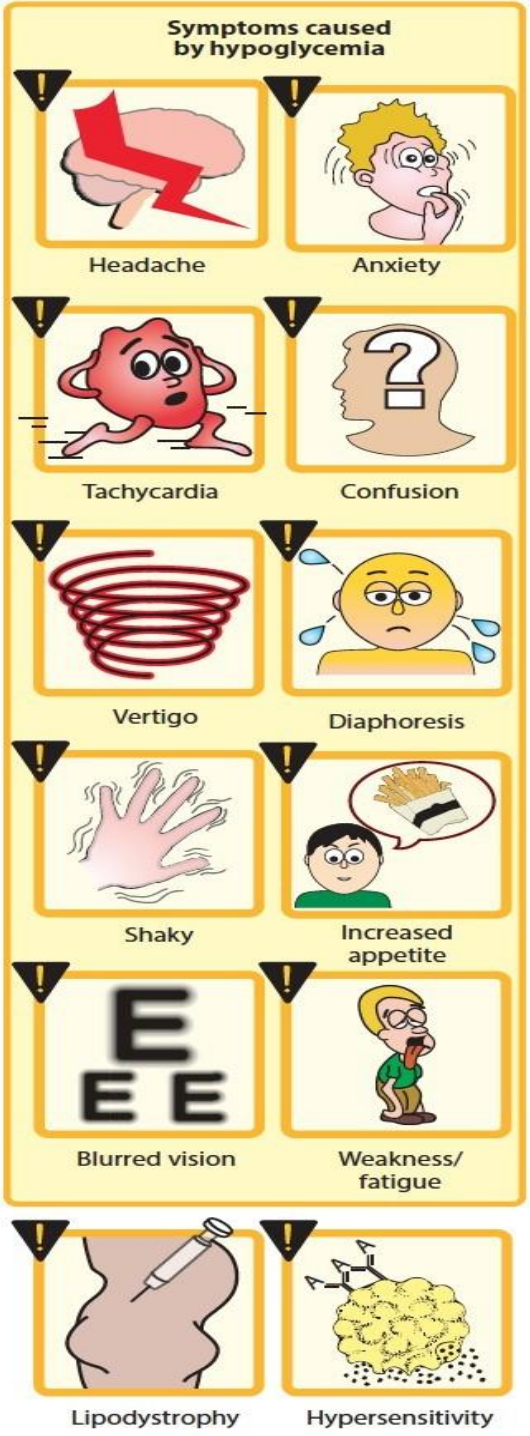
- *Dose, site of injection, blood supply, temperature, and physical activity* can affect the duration of action of the various preparations.

- Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin.

- Insulin is inactivated by insulin-degrading enzyme (also called *insulin protease*), which is found mainly in the liver and kidney.

III- Adverse reactions to insulin

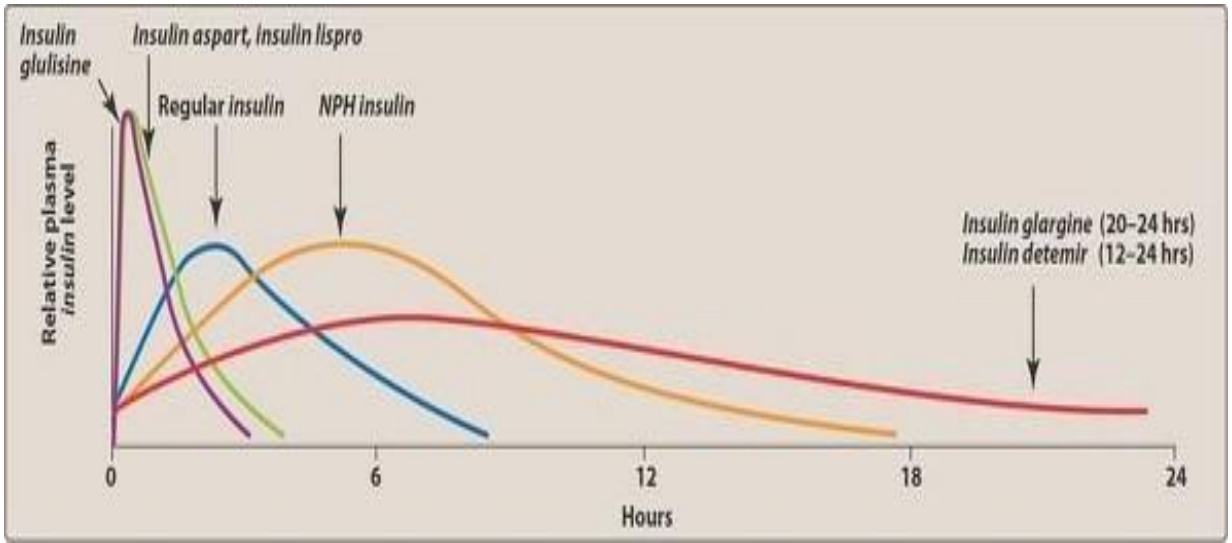
- Hypoglycemia are the most serious and common adverse reactions to an overdose of insulin.
- Other adverse reactions include *weight gain, lipodystrophy, allergic reactions, and local injection site reactions*.
- Diabetics with renal insufficiency may require adjustment of the insulin dose.



IV. Insulin preparations and treatment

A. Rapid-acting and short-acting insulin preparations

- Four insulin preparations fall into this category: *regular insulin, insulin lispro, insulin aspart, and insulin glulisine*.
- Regular insulin is a short-acting, soluble, crystalline zinc insulin.
- Regular insulin is usually given subcutaneously (or intravenously in emergencies), and it rapidly lowers blood glucose.
- Insulin lispro has more rapid absorption after subcutaneous injection than is seen with regular insulin; as a consequence, *insulin lispro acts more rapidly*.



- Peak levels of *insulin lispro* are seen at 30 to 90 minutes after injection, as compared with 50 to 120 minutes for *regular insulin*. Insulin lispro also has a shorter duration of activity.

- *Insulin aspart and insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those *of insulin lispro*.

- Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulin and to control postprandial 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.

- Rapid-acting insulins are commonly used in external insulin pumps, and they are suitable for IV administration, although regular insulin is most commonly used when the IV route is needed.

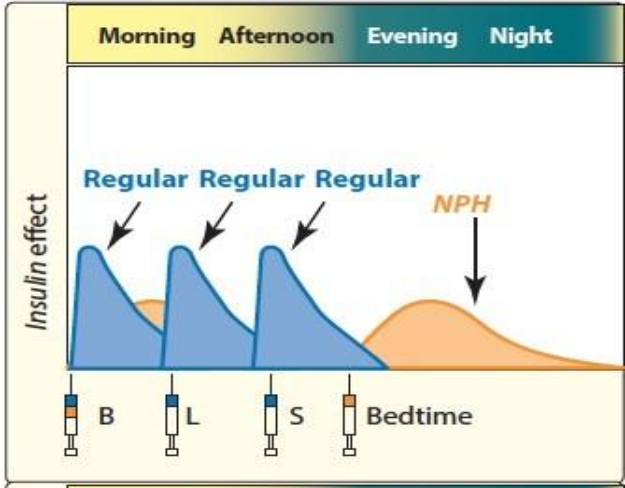
B. Intermediate-acting insulin

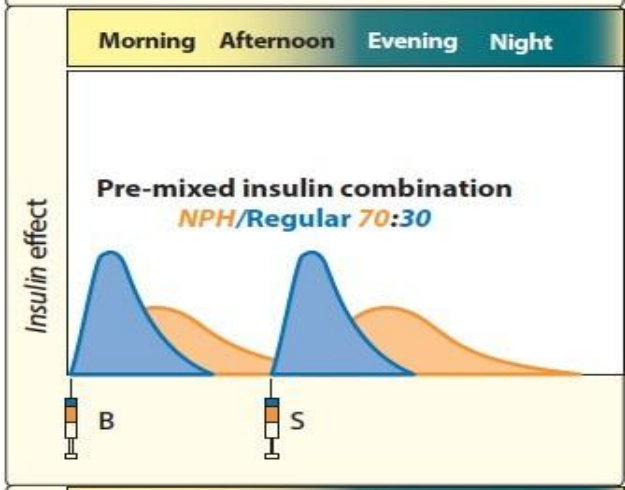
- *Neutral protamine Hagedorn (NPH) insulin* is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine "*insulin isophane*".

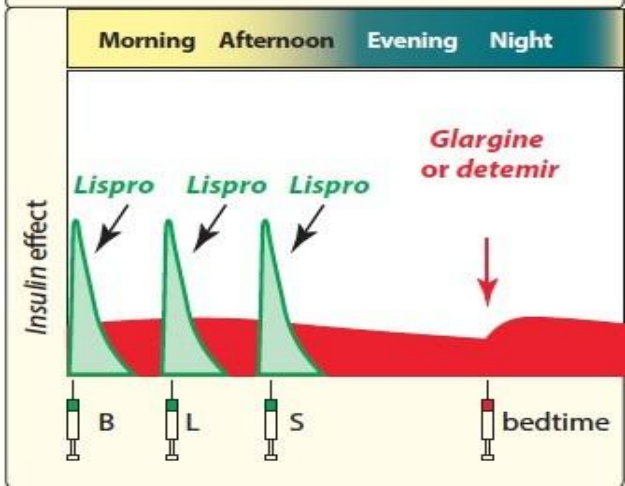
- Its duration of action is intermediate due to delayed absorption of the insulin because of its conjugation with protamine, forming a less-soluble complex.

- 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).







C. Long-acting insulin preparations

- Insulin glargine:

  The isoelectric point of insulin glargine is lower than that of human insulin, leading to precipitation at the injection site, thereby extending its action.

- It is *slower in onset than NPH insulin* and has a flat, prolonged hypoglycemic effect - that is, it has no peak. Like the other insulin preparations, it must be given *subcutaneously*.

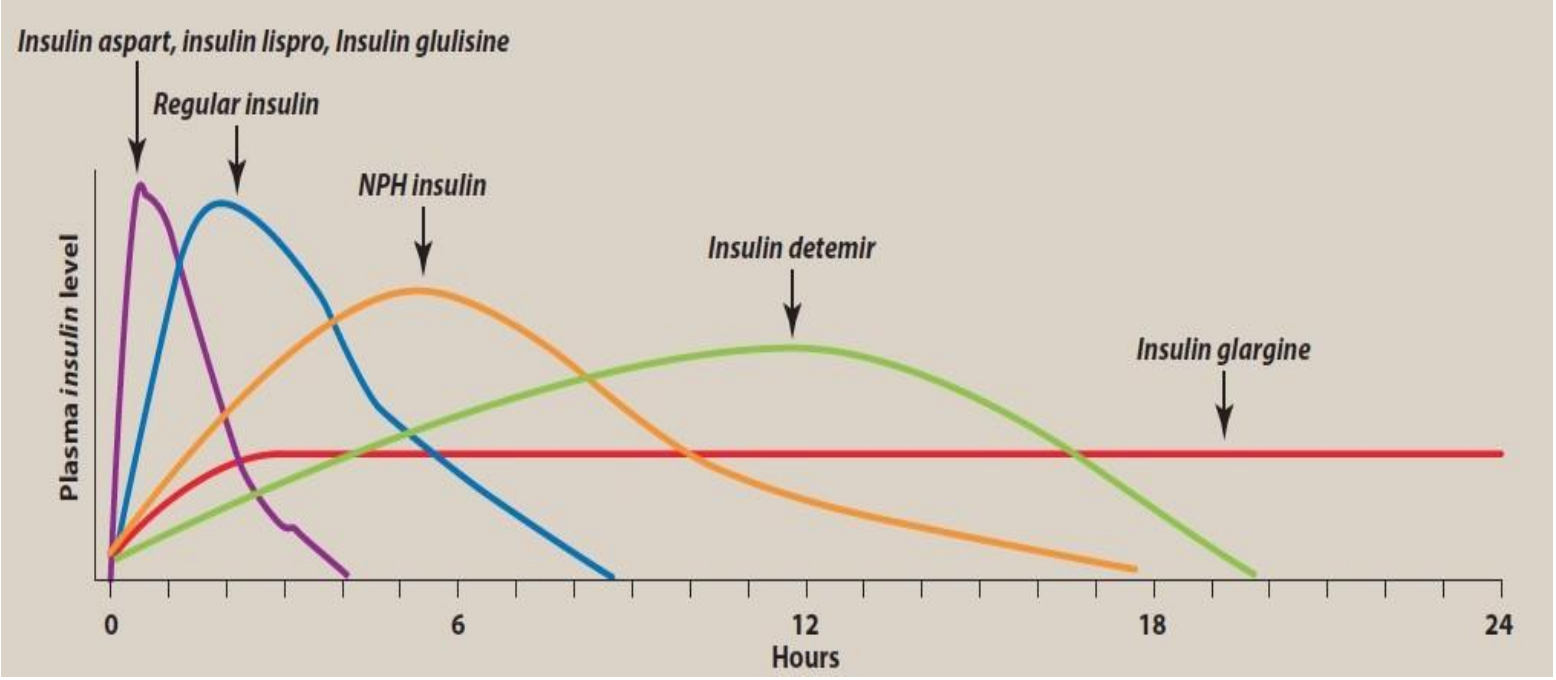
- Insulin detemir:

  It has a fatty-acid side chain. The addition of the fatty-acid side chain enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.

D. Insulin combinations

- Various premixed combinations of human insulins:
- 70% *NPH insulin* plus 30% *regular insulin*, **or** 50% percent of each of these.

- Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.



E. Standard treatment versus intensive treatment

- Standard treatment of patients with diabetes mellitus involves injection of insulin twice daily.

- In contrast, *intensive treatment* seeks to normalize blood glucose through more frequent injections of insulin (three or more times daily in response to monitoring blood glucose levels).

- The American Diabetes Association recommends a target mean blood glucose level of 154 mg/dL or less (HbA1c $\leq$ 7%), and intensive treatment is more likely to achieve this goal.

- Normal mean blood glucose is approximately 115 mg/dL or less, HbA1c < 5.7%.

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- The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive insulin regimens.

- However, patients on intensive therapy show a significant reduction in microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care.

- Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

- Intensive therapy has not been shown to significantly reduce macrovascular complications of diabetes.

V- Synthetic Amylin Analog

- ***Amylin*** is a hormone that is co-secreted with insulin from β cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety.

- ***Pramlintide*** is a synthetic amylin analog that is indicated as an adjunct to mealtime insulin therapy in patients with Type 1 or Type 2 diabetes.

- Pramlintide is administered by *subcutaneous injection* immediately prior to meals.
- When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals to avoid a risk of severe hypoglycemia.

- Pramlintide may not be mixed in the same syringe with any insulin preparation.

- Pramlintide should not be given to patients with diabetic gastroparesis (delayed stomach emptying) hypersensitivity, or hypoglycemic unawareness.

VI. INCRETIN MIMETICS

- Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes.

- The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, in response to a meal.

- Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion.

- Exenatide and liraglutide are injectable incretin mimetics used for the treatment of type 2 diabetes.

VI. INCRETIN MIMETICS

- **Mechanism of action:** The incretin mimetics are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists.
- These agents improve glucose-dependent insulin secretion, slow gastric emptying time, reduce food intake by enhancing satiety, decrease postprandial glucagon secretion, and promote **β**-cell proliferation.
- Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.
- Semaglutide (OZEMPIC),Tirzepatide (mounjaro) are injectable agents.

Pharmacokinetics:

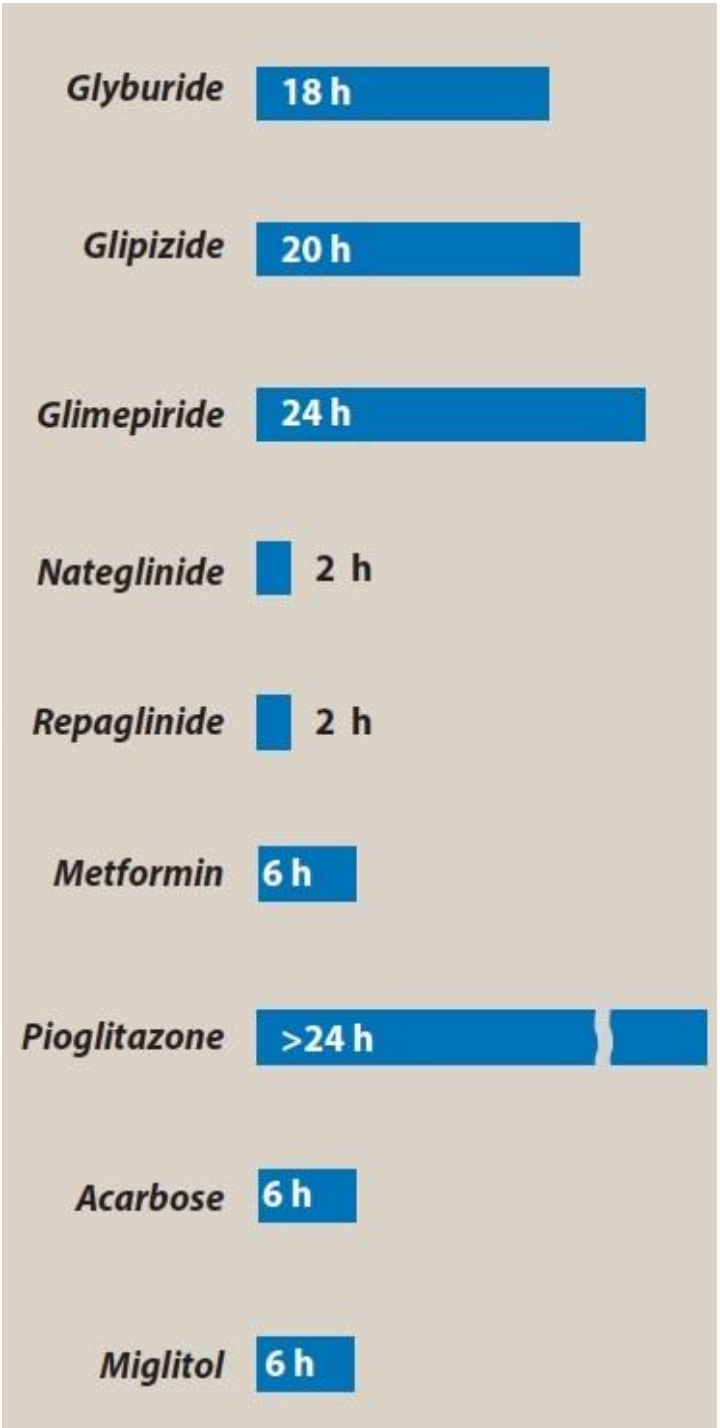
- Exenatide and liraglutide must be administered subcutaneously.
- Liraglutide (VICTOZA) is highly protein bound and has a long half-life, allowing for once-daily dosing without regard to meals.
- Exenatide is eliminated mainly via glomerular filtration and has a much shorter half-life. Because of the short duration of action, exenatide should be injected twice daily within 60 minutes prior to morning and evening meals.
- A once-weekly extended-release preparation is also available. Exenatide should be avoided in patients with severe renal impairment.

VII. 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 hyperglycemia.



A. Sulfonylureas

- These agents are classified as insulin secretagogues, because they promote insulin release from the B2 cells of the pancreas.

- The sulfonylureas in current use are the second-generation drugs, ***Glibenclamide (also known as glyburide), glipizide, and glimepiride***.

- Mechanism of action: Block ATP-sensitive K^+ channels, resulting in depolarization, Ca^{2+} influx, and insulin exocytosis.

- In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.
- The duration of action ranges from 12 to 24 hours.
- **Adverse effects:** Major adverse effects of the sulfonylureas are weight gain, hyperinsulinemia, and hypoglycemia.

B. Glinides

- This class includes ***repaglinide and nateglinide***. Glinides are also considered insulin secretagogues.

Mechanism of action: They bind to a distinct site on the β cell, closing ATP-sensitive K+ channels, and initiating a series of reactions that results in the release of *insulin.*

- 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. This would increase the risk of serious hypoglycemia.

- Glinides should be taken prior to a meal and are well absorbed after oral administration.

C. Biguanides

- ***Metformin***, the only biguanide, 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.
- Metformin also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.

- Weight loss may occur because metformin 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.

Pharmacokinetics and fate: *Metformin* is well absorbed orally, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

Adverse effects: These are largely gastrointestinal. *Metformin* is contraindicated in renal dysfunction due to the risk of lactic acidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of heart failure, sepsis, or other disorders that can cause acute renal failure.

- Hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.
- **Other uses:** Metformin is effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and, possibly, pregnancy.

D. Thiazolidinediones or glitazones

- **Pioglitazone and rosiglitazone** 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 (PPAR-γ), a nuclear hormone receptor.

- Activation of PPAR-γ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.
- Rosiglitazone increases LDL cholesterol and triglycerides, whereas pioglitazone decreases triglycerides. Both drugs increase HDL cholesterol.

D. Thiazolidinediones or glitazones

- 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 second- or third-line agent for type 2 diabetes.

- **Pharmacokinetics:** No dosage adjustment is required in renal impairment.
- These agents should be avoided in nursing mothers.

- **Adverse effects:** Potential increased risk of myocardial infarction and death from cardiovascular causes with rosiglitazone. As a result, use of rosiglitazone was limited to patients enrolled in a special restricted access program. After a further review of safety data, the restrictions on rosiglitazone use were subsequently lifted.

- **Other uses:** As with *metformin*, the relief of *insulin* resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.

E. α-Glucosidase Inhibitors

- ***Acarbose*** and ***miglitol*** are orally active drugs used for the treatment of patients with 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 hypoglycemia when used as monotherapy.

- However, when used with *insulin* secretagogues or *insulin*, hypoglycemia may develop.

F. Dipeptidyl peptidase-4 inhibitors (DPP-4)

- ***Alogliptin*** (Nesina, Kazano), ***linagliptin*** (Tradjenta), ***saxagliptin*** (Onglyza, Kombiglyze XR), ***and sitagliptin*** (Januvia, Janumet), are orally active dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

- **Mechanism of action:** These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1. Prolonging the activity of incretin hormones increases insulin release in response to meals and reduces inappropriate secretion of glucagon.

- DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, TZDs, or insulin.

- Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.
- **Pharmacokinetics:** Food does not affect the extent of absorption.
- All DPP-4 inhibitors except **linagliptin** require dosage adjustments in renal dysfunction.

G. Sodium–glucose cotransporter 2 inhibitors (SGLT- 2i)

- ***Canagliflozin and dapagliflozin*** are the agents in this category of drugs for type 2 diabetes.
- **Mechanism of action:** The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.

- Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

- **Pharmacokinetics:** These agents are given once daily in the morning.

- Canagliflozin should be taken before the first meal of the day.

- **Adverse effects:** female genital mycotic infections (for example, vulvovaginal candidiasis), urinary tract infections, and urinary frequency.

H. Other agents

- Both the dopamine agonist bromocriptine and the bile acid sequestrant colesevelam produce modest reductions in HbA1c. The mechanism of action of glucose lowering is unknown for both of these drugs.
- Although bromocriptine and colesevelam are indicated for the treatment of type 2 diabetes, their modest efficacy, adverse effects, and pill burden limit their use in clinical practice.


Thank You!