Drugs for Diabetes

Part 1

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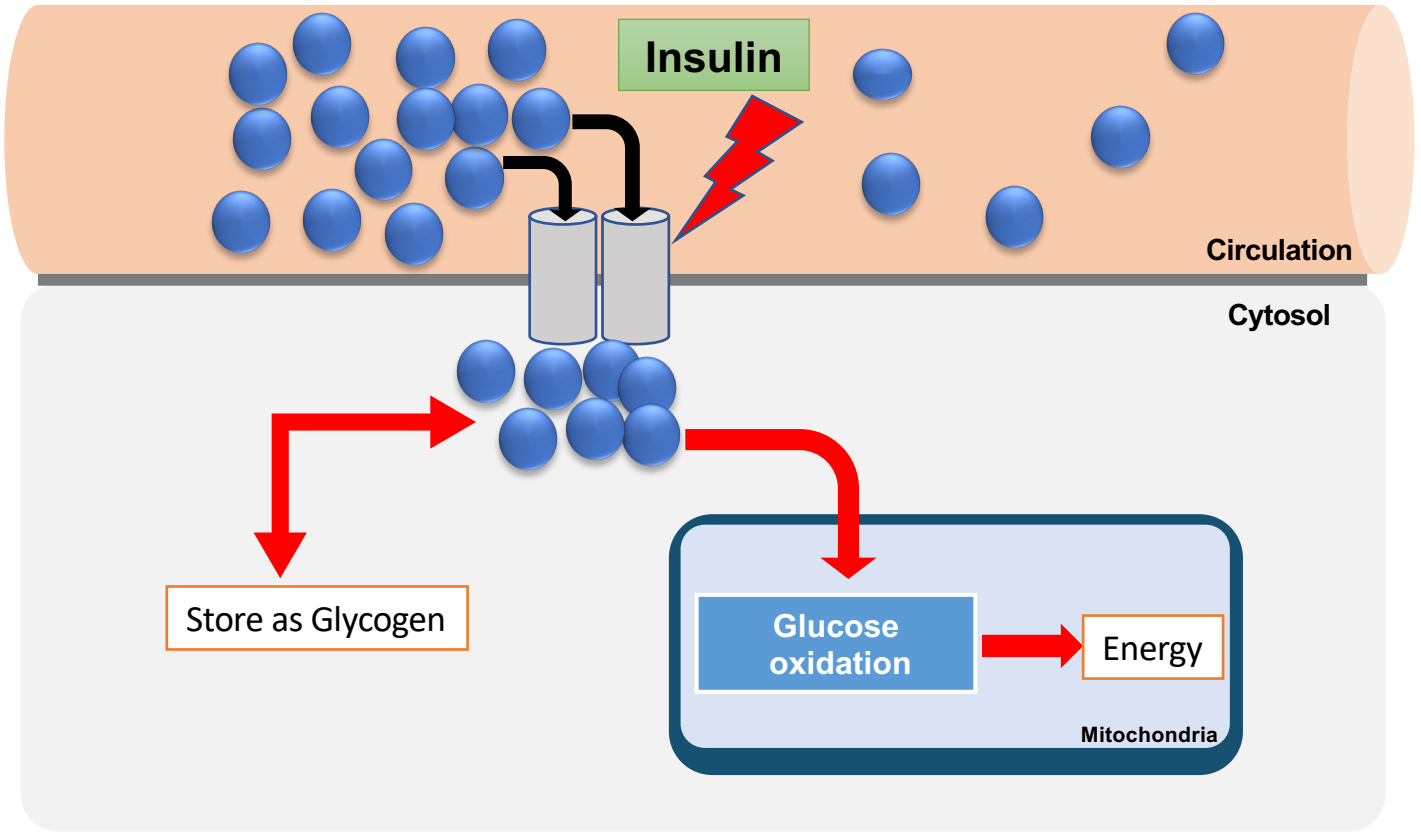
Mechanism of Action of Insulin



Diabetes Mellitus

- 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 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

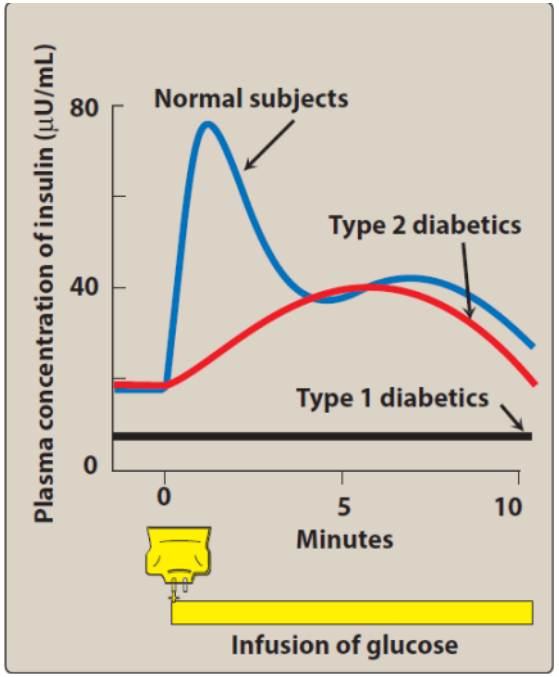
A. Type 1 diabetes

- **Cause:** Loss of Beta (β)-cell function is usually ascribed to autoimmune-mediated processes directed against the β-cell, and it may be triggered by an invasion of viruses or the action of chemical 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 the *catabolic state* that results from and is characterized by *hyperglycemia and life-threatening ketoacidosis*.



B. 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.

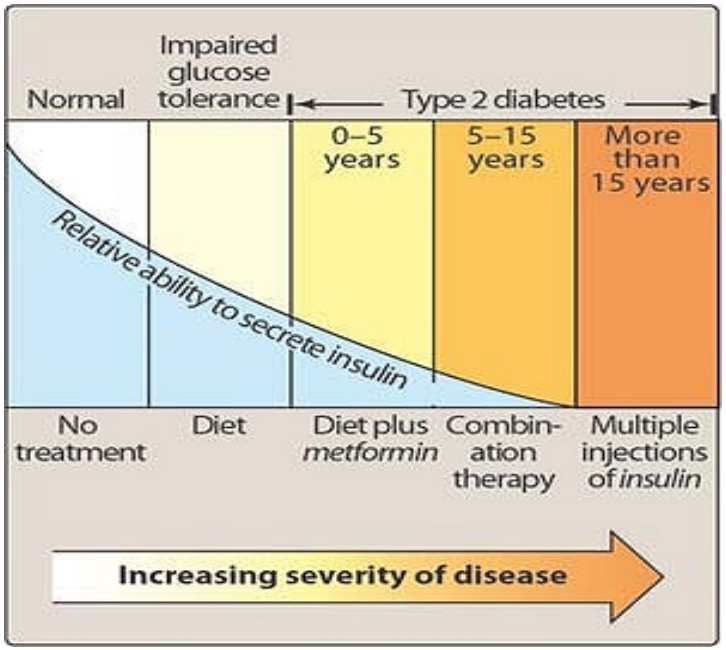
Treatment of Type-2 Diabetes

- 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 are dependent on 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



B. Sources of insulin

- 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:

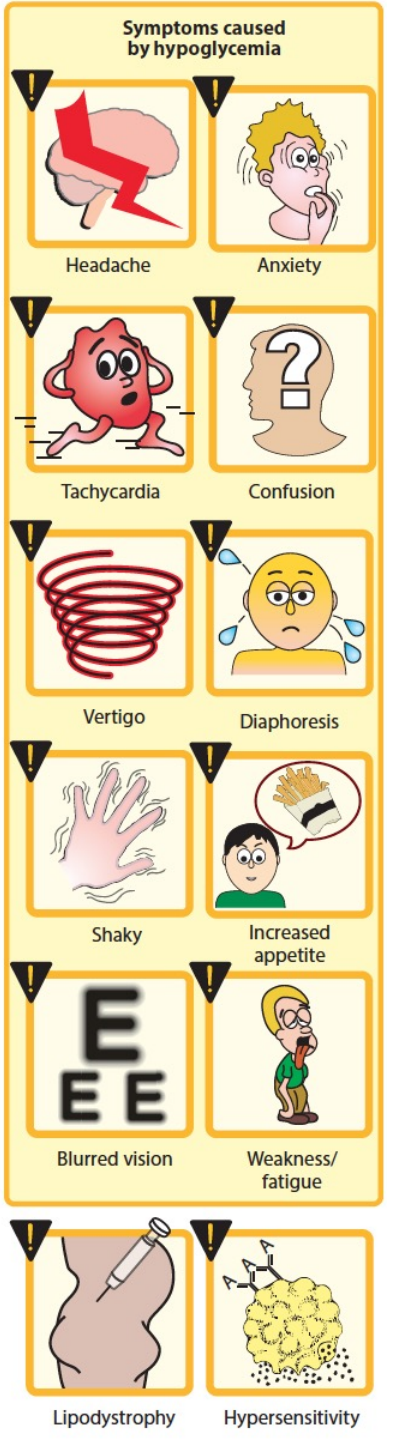
1. *Lispro, Aspart, and Glulisine* - have a faster onset and shorter duration of action than regular insulin, because they do not aggregate or form complexes.
2. Glargine and Detemir are long-acting insulins and show prolonged, flat levels of the hormone following injection.

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

D. 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

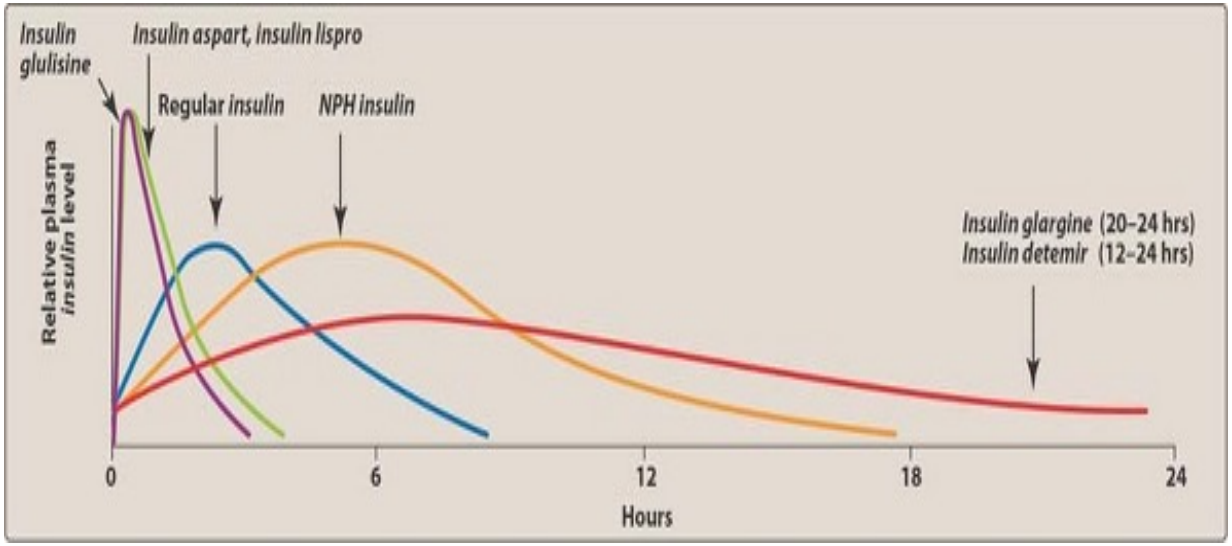
A. Rapid-acting and short-acting insulin preparations

- 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.

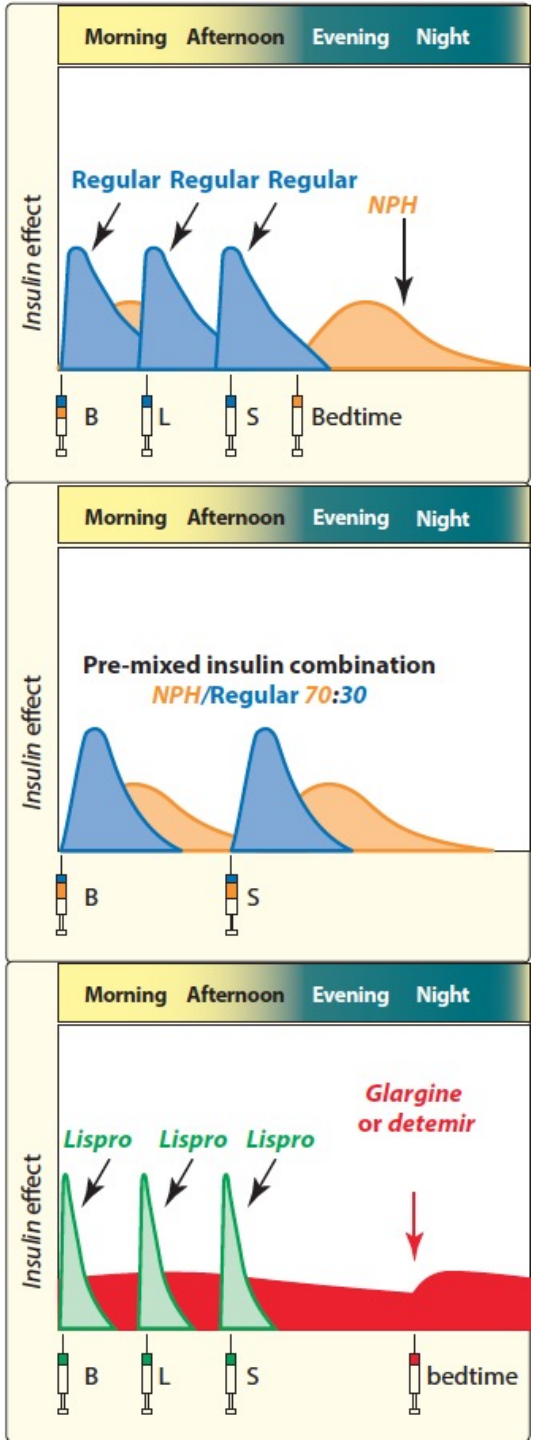
B. Intermediate-acting insulin

- *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

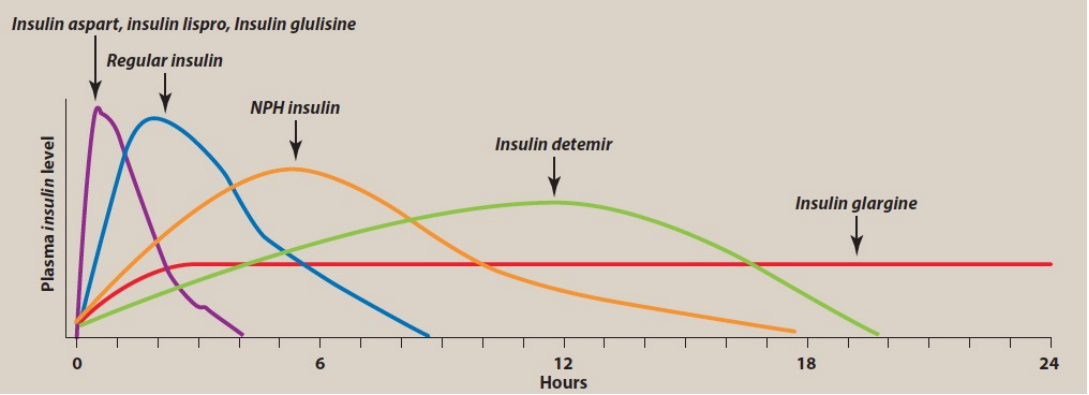
- Insulin glargine:

  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 ≤ 7%), and intensive treatment is more likely to achieve this goal.
- Normal mean blood glucose is approximately <100 mg/dL or less, HbA1c < 5.7%.
- 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.

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.


Thank You!