Pancreatic Hormones
&
Antidiabetic Drugs

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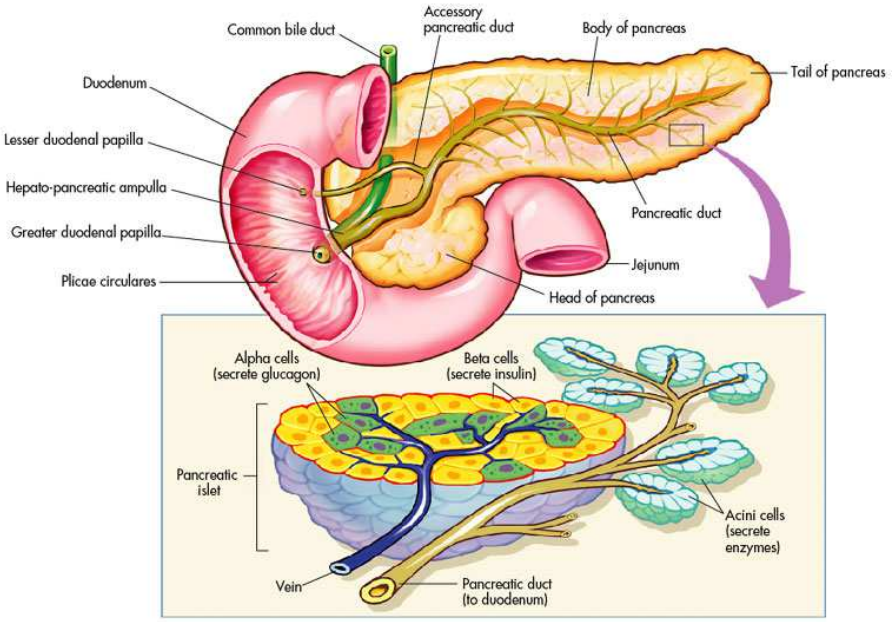
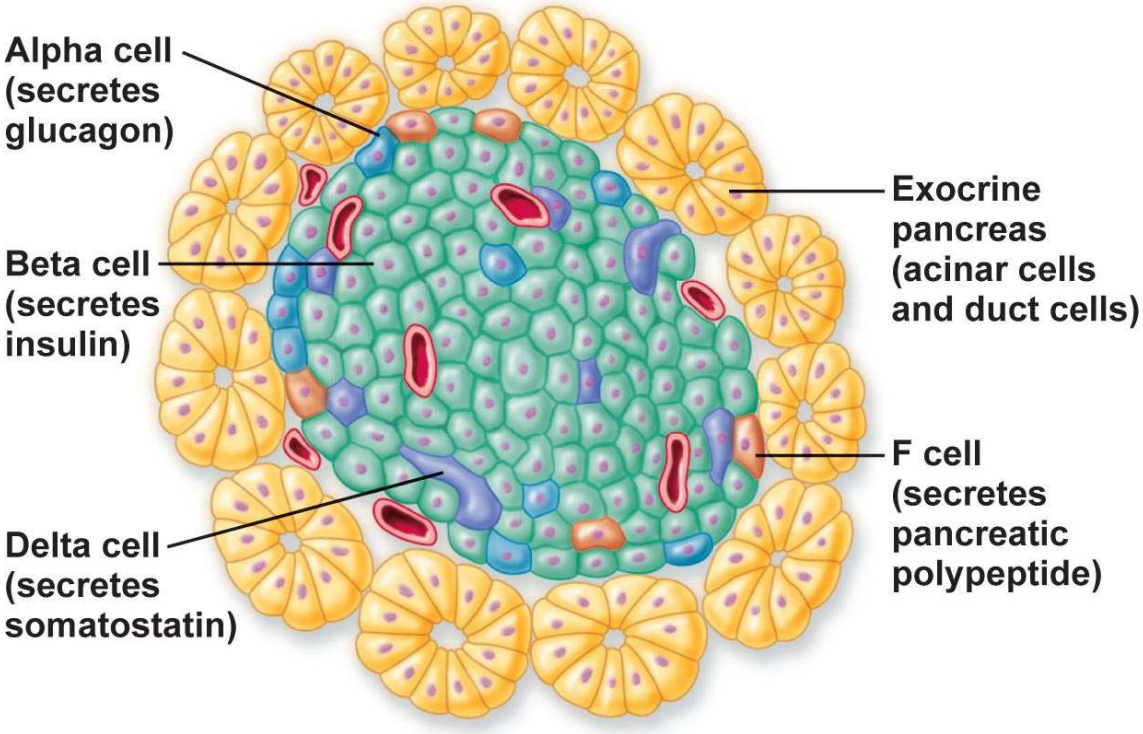
12/ 03/ 2016

Endocrine Pancreas



(From Thibodeau GA, Patton K: *Anatomy & physiology*, ed 5, St Louis, 2003, Mosby.)



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The Endocrine Pancreas

➢ The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans interspersed throughout the pancreatic gland.

➢ Within the islets, at least four hormone-producing cells are present.

➢ Their hormone products include:

- o **insulin**, the storage and anabolic hormone of the body;
- o **glucagon**, the hyperglycemic factor that mobilizes glycogen stores;
- o **somatostatin**, a universal inhibitor of secretory cells;
- o and **pancreatic peptide**, a small protein that facilitates digestive processes by a mechanism not yet clarified.

➢ The elevated blood glucose associated with diabetes mellitus results from absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action.

➢ The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories:

- type 1, "insulin-dependent diabetes,"
- type 2, "noninsulin-dependent diabetes,"
- type 3, "other,"
- and type 4, "gestational diabetes mellitus".

Type 1 Diabetes Mellitus

➢ The hallmark of type 1 diabetes is selective B cell destruction and severe or absolute insulin deficiency.

➢ Administration of insulin is essential in patients with type 1 diabetes.

➢ Type 1 diabetes is further subdivided into immune and idiopathic causes.

➢ The immune form is the most common form of type 1 diabetes.

➢ Although most patients are younger than 30 years of age at the time of diagnosis, the onset can occur at any age.

➢ Type 1 diabetes is found in all ethnic groups, but the highest incidence is in people from northern Europe.

➢ Susceptibility appears to involve a multi-factorial genetic linkage but only 15-20% of patients have a positive family history.

Type 1 Diabetes Mellitus

Pharmacotherapy

- Appropriate substitution therapy with exogenous insulin or insulin analogues is a must (IDDM) to avoid:
  - acute complications
    - diabetic ketoacidosis (potentially life-threatening)
  - chronic complications
    - peripheral neuropathies,
    - microangiopathies (nephropathies, retinopathies)
    - macroangiopathies (accelerated atherosclerosis which leads into myocardial ischemia, cerebral ischemia, lower extremity ischemia…)
- AIM: to maintain blood glucose as close to normal as possible, and to avoid wide swings in their levels (that contribute to long-term complications).

Type 2 Diabetes Mellitus

- Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a relative deficiency in insulin secretion.
- Although insulin is produced by the B cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises.
- The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels, and reciprocally low (HDL) levels.
- Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control the blood glucose.
- It is likely that 10–20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and type 2, or have a slowly progressing type 1, and ultimately will require full insulin replacement.

Type 2 Diabetes Mellitus

- Although persons with type 2 diabetes ordinarily will not develop ketosis, ketoacidosis may occur as the result of stress such as infection or use of medication that enhances resistance, eg, corticosteroids.
- Dehydration in untreated and poorly controlled individuals with type 2 diabetes can lead to a life-threatening condition called "non-ketotic hyperosmolar coma".
- In this condition, the blood glucose may rise to 6–20 times the normal range and an altered mental state develops or the person loses consciousness.
- Urgent medical care and rehydration is required.

Type 3 Diabetes Mellitus

- The type 3 designation refers to multiple other specific causes of an elevated blood glucose: nonpancreatic diseases, drug therapy, etc.

Type 4 Diabetes Mellitus

- Gestational Diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy.
- Gestational diabetes is diagnosed in approximately 4% of all pregnancies in the USA.
- During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester.
- Risk assessment for diabetes is suggested starting at the first prenatal visit.
- Screening may be deferred in lower risk women until the 24th to 28th week of gestation.

Diabetes diagnosis and glycemia

- 80 to 90 mg per 100 ml, is the normal fasting blood glucose concentration in humans and most mammals which is associated with very low levels of insulin secretion.

Fasting Plasma Glucose Test (FPG) - (cheap, fast)
*fasting B.G.L. 100-125 mg/dl signals pre-diabetes
*>126 mg/dl signals diabetes

Oral Glucose Tolerance Test (OGTT)
*tested for 2 hrs after glucose-rich drink
*140-199 mg/dl signals pre-diabetes
*>200 mg/dl signals diabetes

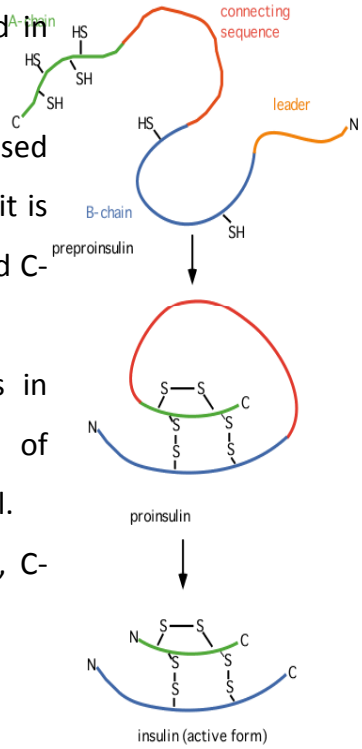
Hb A1c: Glycated Hemoglobin tests

Treatment with Insulin

- The current classification of diabetes mellitus identifies a group of patients who have virtually no insulin secretion and whose survival depends on administration of exogenous insulin.
- This insulin dependent group (type 1) represents 5–10% of the diabetic population in the USA.
- Most type 2 diabetics do not require exogenous insulin for survival, but many need exogenous supplementation of their endogenous secretion to achieve optimum health.
- It is estimated that as many as 20% of type 2 diabetics in the USA are presently taking insulin.

Insulin

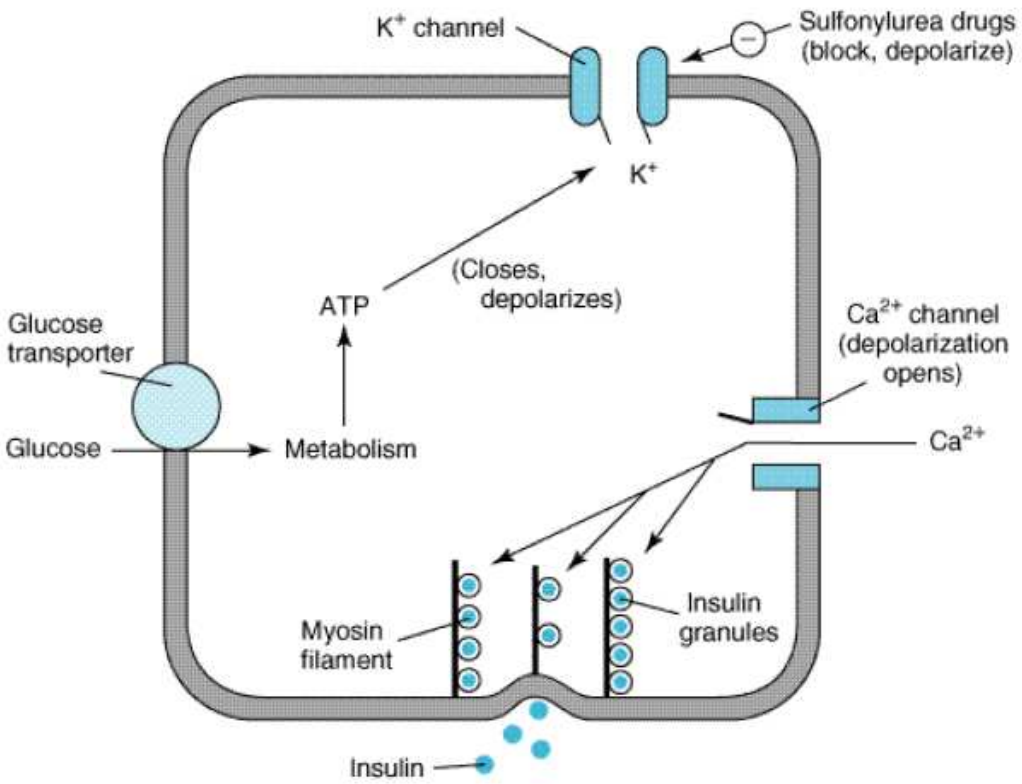
Chemistry



- Insulin is a small protein, contains 51 amino acids arranged in two chains (A and B) linked by disulfide bridges.
- Proinsulin, a long single-chain protein molecule, is processed within the Golgi apparatus and packaged into granules, where it is hydrolyzed into insulin and a residual connecting segment called C-peptide.
- Insulin and C-peptide are secreted in equimolar amounts in response to all insulin secretagogues; a small quantity of unprocessed or partially hydrolyzed proinsulin is released as well.
- While proinsulin may have some mild hypoglycemic action, C-peptide has no known physiologic function.

Insulin Secretion

- Insulin is released from pancreatic B cells at a low basal rate and at a much higher stimulated rate in response to a variety of stimuli, especially glucose.
- Other stimulants such as other sugars (eg, mannose), certain amino acids (eg, leucine, arginine), and vagal activity are recognized.
- Hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels.
- Decreased outward potassium efflux results in depolarization of the B cell and opening of voltage-gated calcium channels.
- The resulting increased intracellular calcium triggers secretion of the hormone.
- The insulin secretagogue drug group (sulfonylureas, meglitinides, and D-phenylalanine) exploits parts of this mechanism.

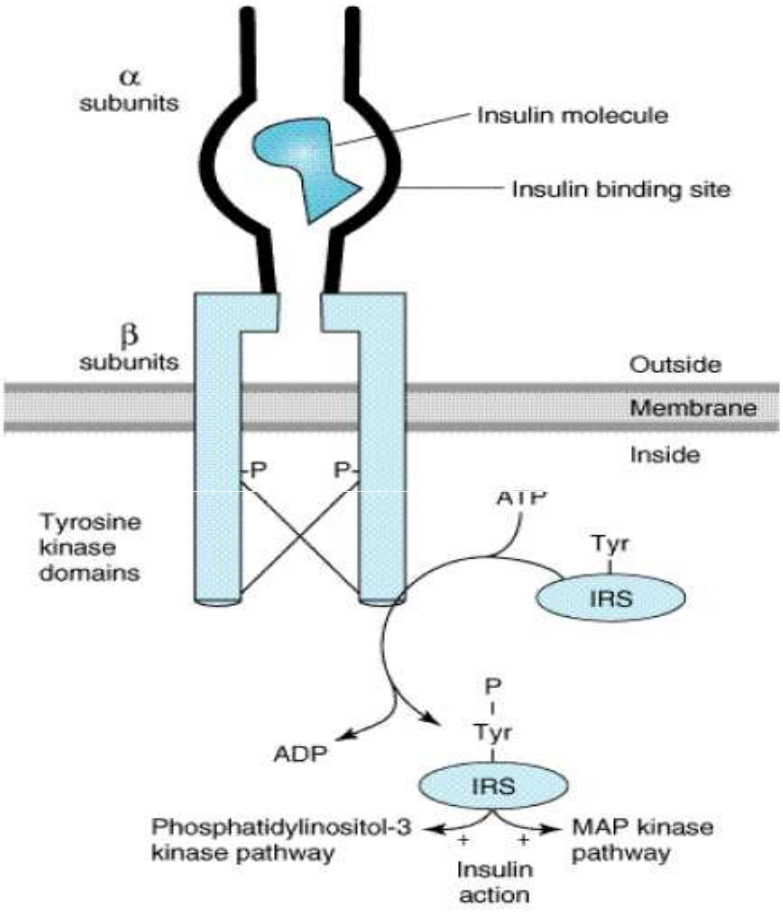


Insulin Degradation

- The liver and kidney are the two main organs that remove insulin from the circulation.
- The liver normally clears the blood of approximately 60% of the insulin released from the pancreas by virtue of its location as the terminal site of portal vein blood flow, with the kidney removing 35–40% of the endogenous hormone.
- However, in insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed, with as much as 60% of exogenous insulin being cleared by the kidney and the liver removing no more than 30–40%.
- The half-life of circulating insulin is 3–5 minutes.

The Insulin Receptor

- Once insulin has entered the circulation, it is bound by specialized receptors that are found on the membranes of most tissues.
- The biologic responses promoted by these insulin-receptor complexes have been identified in the primary target tissues, ie, liver, muscle, and adipose tissue.
- The receptors bind insulin with high specificity and affinity in the picomolar range.
- The full insulin receptor consists of two covalently linked heterodimers, each containing an subunit, which is entirely extracellular and constitutes the recognition site, and a subunit that spans the membrane (contains a tyrosine kinase).
- The binding of an insulin molecule to the subunits at the outside surface of the cell activates the receptor and thereby facilitates phosphorylation of tyrosine residues and tyrosine kinase activity.



Schematic diagram of the insulin receptor heterodimer in the activated state. IRS, insulin receptor substrate; tyr, tyrosine; P, phosphate.

➢ The network of phosphorylations within the cell results in multiple effects including translocation of glucose transporters (especially GLUT-4) to the cell membrane with a resultant increase in glucose uptake; glycogen synthase activity and increased glycogen formation; multiple effects on protein synthesis, lipolysis, and lipogenesis; and activation of transcription factors that enhance DNA synthesis and cell growth and division.

➢ Various hormonal agents (eg, glucocorticoids) lower the affinity of insulin receptors for insulin; growth hormone in excess increases this affinity slightly.

Endocrine Effects of Insulin.

➢ Effect on liver:

- *Reversal of catabolic features of insulin deficiency*
  - Inhibits glycogenolysis
  - Inhibits conversion of fatty acids and amino acids to keto acids
  - Inhibits conversion of amino acids to glucose

- *Anabolic action*
  - Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
  - Increases triglyceride synthesis and very low density lipoprotein formation.

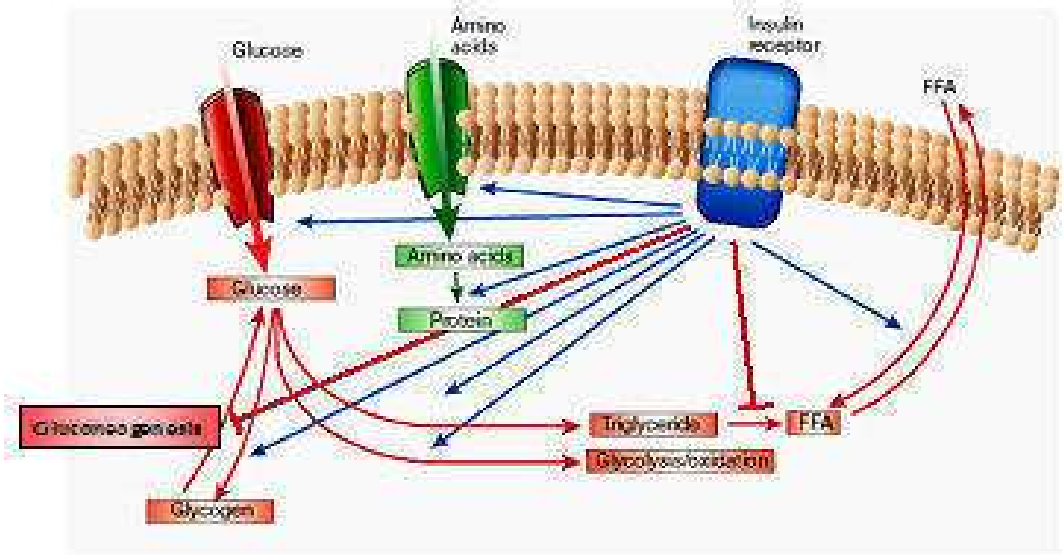
➢ **Effect on muscle:**

- Increased protein synthesis
  - •Increases amino acid transport
  - •Increases ribosomal protein synthesis
- Increased glycogen synthesis
  - •Increases glucose transport
  - •Induces glycogen synthase and inhibits phosphorylase.

➢ **Effect on adipose tissue:**

- Increased triglyceride storage
- Lipoprotein lipase is activated by insulin to hydrolyze TGs from lipoproteins
- Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
- Intracellular lipase is inhibited by insulin

Actions of Insulin



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

Characteristics of Available Insulin Preparations

- Commercial insulin preparations differ in a number of ways, including differences in the recombinant DNA production techniques, amino acid sequence, concentration, solubility, and the time of onset and duration of their biologic action.

Principal Types and Duration of Action of Insulin Preparations

- Four principal types of insulins are available:
  (1) rapid-acting, with very fast onset and short duration;
  (2) short-acting, with rapid onset of action;
  (3) intermediate-acting;
  (4) long-acting, with slow onset of action.

- Rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amounts of zinc to improve their stability and shelf-life.
- All other commercial insulins have been modified to provide prolonged action and are, with the exception of insulin glargine, dispensed as turbid suspensions at neutral pH with either protamine in phosphate buffer (neutral protamine Hagedorn [NPH] insulin) or varying concentrations of zinc in acetate buffer (ultralente and lente insulins).
- Insulin glargine is the only soluble long-acting insulin.

Principal Types and Duration of Action of Insulin Preparations

- The goal of subcutaneous insulin therapy is to replace the normal basal (overnight, fasting, and between meal) as well as prandial (mealtime) insulin.
- Current regimens generally use intermediate- or long-acting insulins to provide basal or background coverage, and rapid-acting or short-acting insulin to meet the mealtime requirements as supplemental doses to correct high blood sugars.
- Intensive therapy ("tight control") attempts to restore near-normal glucose patterns throughout the day while minimizing the risk of hypoglycemia.
- The most sophisticated insulin regimen delivers rapid-acting insulin through a continuous subcutaneous insulin infusion device; alternative intensive regimens referred to as multiple daily injections (MDI) use long-acting or intermediate-acting insulins with multiple boluses of rapid-acting or short-acting insulin.
- Conventional therapy presently consists of split-dose injections of mixtures of rapid- or short-acting and intermediate-acting insulins.

Preparation Species Source Concentration

Rapid-acting insulins
Insulin lispro, Humalog (Lilly) Human analog U100
Insulin Aspart, Novolog (Novo Nordisk) Human analog U100

Short-acting insulins
Regular (Novo Nordisk) Human U100
Regular Humulin (Lilly) Human U100, U500
Velosulin BR (Novo Nordisk) Human U100

Intermediate-acting insulins
Lente Humulin (Lilly) Human U100
Lente (Novo Nordisk) Human U100
NPH Humulin (Lilly) Human U100
NPH (Novo Nordisk) Human U100

Premixed insulins (% NPH, % regular)
Novolin 70/30 (Novo Nordisk) Human U100
Humulin 70/30 and 50/50 (Lilly) Human U100

Premixed (% NP-analog, % rapid acting analog) Human analog U100
50/50 NPL, Lispro (Lilly) Human analog U100
75/25 NPL, Lispro (Lilly) Human analog U100
70/30 NPA, Aspart (NovoNordisk) Human analog U100

Long-acting insulins
Ultralente Humulin U (Lilly) Human U100
Insulin glargine-lantus (Aventis/Hoechst Marion Roussel) Human U100

Rapid-Acting Insulin

- Two rapid-acting insulin analogs are commercially available: **insulin lispro and insulin aspart.**
- The rapid-acting insulins permit more physiologic prandial insulin replacement because their rapid onset and early peak action more closely mimics normal endogenous prandial insulin secretion than does regular insulin, and they have the additional benefit of allowing insulin to be taken immediately before the meal without sacrificing glucose control.
- Their duration of action is rarely more than 3–5 hours, which decreases the risk of late postmeal hypoglycemia.
- They have the lowest variability of absorption of all available insulin formulations.

- Insulin lispro and aspart , when injected subcutaneously quickly dissociate into monomers and are rapidly absorbed with onset of action within (5–15 min for Insulin lispro, 10–20 min for Insulin aspart) and reaching peak activity as early as 1 hour.

- Although not specifically approved for use in continuous subcutaneous insulin infusion (CSII) pumps, when used in these devices or in intensive insulin regimens, insulin lispro is associated with significantly improved glycemic control compared with regular insulin, without increased incidence of hypoglycemia.

- Insulin aspart is approved for subcutaneous administration by injection as well as through CSII devices.

Short-Acting Insulin

➢ Regular insulin is a short-acting soluble crystalline zinc insulin made by recombinant DNA techniques to produce a molecule identical to human insulin.

➢ Its effect appears within 30 minutes and peaks between 2 and 3 hours after subcutaneous injection and generally lasts 5–8 hours.

➢ In high concentrations, regular insulin molecules self-aggregate to form dimers that stabilize around zinc ions to create insulin hexamers. The hexameric nature of regular insulin causes a delayed onset and prolongs the time to peak action.

➢ As the insulin depot is diluted by interstitial fluid and the concentration begins to fall, the hexamers break down into dimers and finally monomers.

➢ Short-acting soluble insulin is the only type that should be administered *i.v* as the dilution causes the hexameric insulin to immediately dissociate into monomers.

➢ It is particularly useful for intravenous therapy in the management of diabetic ketoacidosis and when the insulin requirement is changing rapidly, such as after surgery or during acute infections.

Intermediate-Acting and Long-Acting Insulins

Lente Insulin

➢ Lente insulin is a mixture of 30% semilente (has a relatively rapid onset of action) with 70% ultralente insulin (a poorly soluble crystal of zinc insulin that has a delayed onset and prolonged duration of action).

➢ These two components provide a combination of relatively rapid absorption with sustained long action, making lente insulin a useful therapeutic agent.

➢ As with regular insulin, the time of onset, time to peak, and duration of action are dose-dependent.

NPH (Neutral Protamine Hagedorn, or Isophane) Insulin

- NPH insulin is an intermediate-acting insulin wherein absorption and the onset of action is delayed by combining appropriate amounts of insulin and protamine (arginine-rich peptides)so that neither is present in an uncomplexed form ("isophane").
- After subcutaneous injection, proteolytic tissue enzymes degrade the protamine to permit absorption of insulin.
- The onset and duration of action of NPH insulin are similar to those of lente insulin; it is usually mixed with regular, lispro, or aspart insulin and given two to four times daily for insulin replacement in patients with type 1 diabetes.

Ultralente Insulin

- There has recently been a resurgence in the use of ultralente insulin, in combination with multiple injections of rapid-acting insulin, as a means of attempting optimal control in patients with type 1 diabetes.

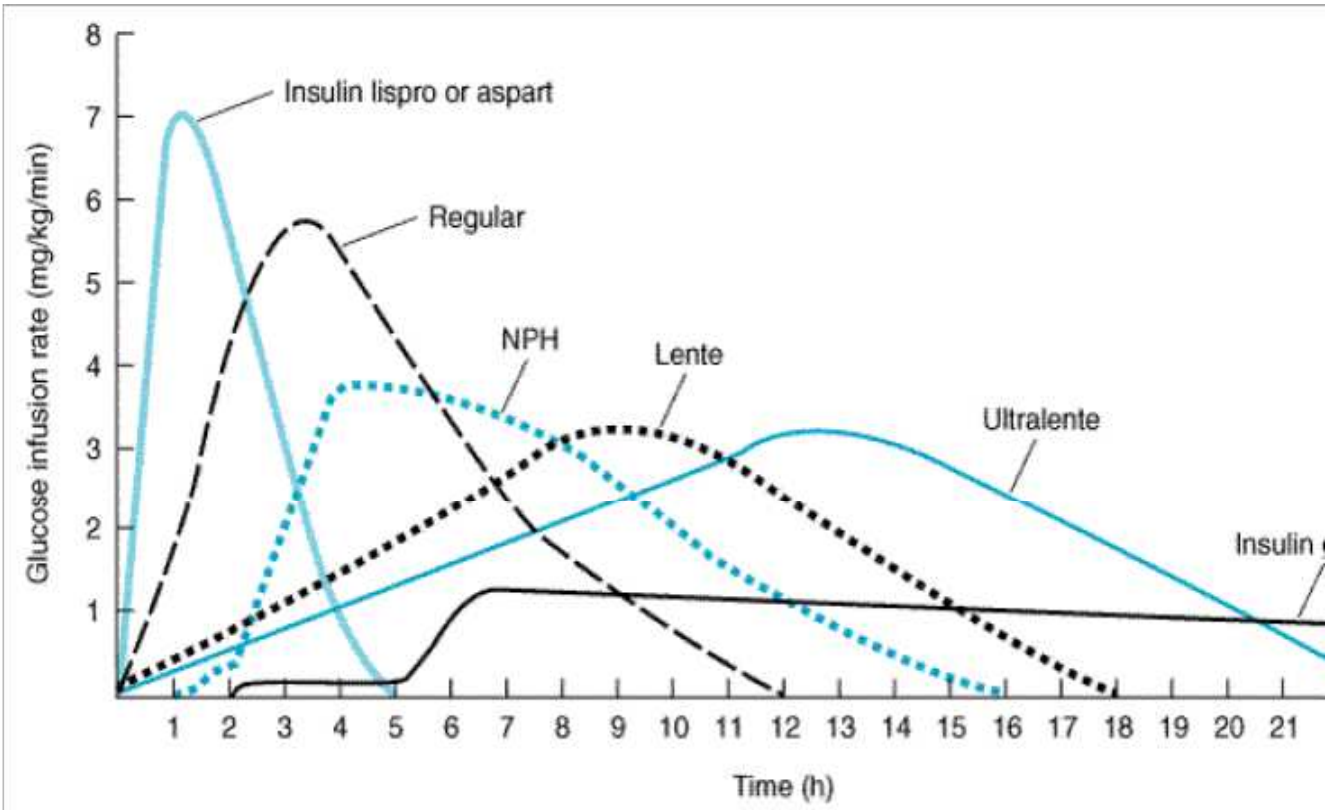
- This is needed in patients with type 1 diabetes to achieve basal insulin levels throughout the 24 hours that are more comparable to those achieved in normal subjects by basal endogenous secretion or by the overnight infusion rate programmed into insulin pumps.

Insulin Glargine

- Insulin glargine is a soluble, "peakless" (ie, having a broad plasma concentration plateau), ultralong- acting insulin analog.
- This product was designed to provide reproducible, convenient, background insulin replacement.
- An analog that is soluble in solution but precipitates in the more neutral body pH after subcutaneous injection.
- Individual insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin.
- Insulin glargine has a slow onset of action (1–1.5 hours) and achieves a maximum effect after 4–5 hours, which is maintained for 11–24 hours or longer.
- Glargine is usually given once daily, although some very insulin-sensitive individuals will benefit from split (twice a day) dosing.

Mixtures of Insulins

- Since intermediate-acting insulins require several hours to reach adequate therapeutic levels, their use in type 1 diabetic patients requires supplements of lispro, aspart, or regular insulin before meals. For convenience, these are often mixed together in the same syringe before injection.
- Insulin lispro and aspart can be acutely mixed (ie, just before injection) with either NPH, lente, or ultralente insulin without affecting their rapid absorption.
- Insulin glargine must be given as a separate injection. It is not miscible acutely or in a premixed preparation with any other insulin formulation.



Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg; with the exception of insulin lispro and insulin aspart, duration increases considerably when dosage is increased.

Insulin Delivery Systems

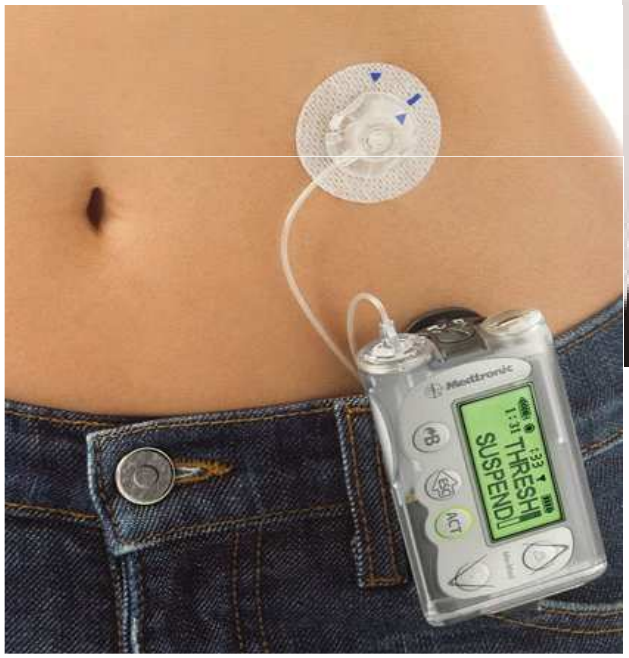
- The standard mode of insulin therapy is subcutaneous injection using conventional disposable needles and syringes.
- During the last 3 decades, much effort has gone into exploration of other means of administration.

Portable Pen Injectors

- To facilitate multiple subcutaneous injections of insulin, particularly during intensive insulin therapy, portable pen-sized injectors have been developed.
- These contain cartridges of insulin and replaceable needles.
- These include regular insulin, insulin lispro, insulin aspart, NPH insulin, and premixed 70%/30% and 50%/50% NPH/regular, 75% NPL/25% lispro, 50% NPL/50% lispro, and 70% NPA/30% aspart insulin.
- They have been well accepted by patients because they eliminate the need to carry syringes and bottles of insulin to the workplace and while traveling.

Continuous Subcutaneous Insulin Infusion Devices (Csii, Insulin Pumps)

- Insulin Pumps 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.
- The bolus amounts frequently vary and are used to correct high blood glucose levels and to cover mealtime insulin requirements based on the carbohydrate content of the food and concurrent activity.
- It is usually placed on a belt or in a pocket, and the insulin is infused through thin plastic tubing that is connected to the subcutaneously inserted infusion set.
- Velosulin and insulin aspart are the only insulins specifically approved for pump use.
- Although not formally approved for pump use, insulin lispro has been successfully delivered through CSII devices since it became commercially available.
- Insulins aspart and lispro are preferred pump insulins because their favorable pharmacokinetic attributes allow glycemic control without increasing the risk of hypoglycemia.



Inhaled Insulin

- Clinical trials are in progress to evaluate the safety and efficacy of finely powdered and aerosolized insulin formulations delivered by inhalation.
- Insulin is readily absorbed into the bloodstream through alveolar walls, but the challenge has been to create particles that are small enough to pass through the bronchial tree without being trapped and still enter the alveoli in sufficient amounts to have a clinical effect.
- Insulin delivered by the inhaled route should have a rapid onset and a relatively short duration of action and could be used to cover mealtime insulin requirements or to correct high glucose levels, but not to provide background or basal insulin coverage.
- Safety concerns regarding pulmonary fibrosis or hypertension and excessive antibody formation may preclude or delay approval.

Complications of Insulin Therapy

Hypoglycemia

- Hypoglycemic reactions are the most common complication of insulin therapy.
- They may result from a delay in taking a meal, inadequate carbohydrate consumed, unusual physical exertion, or a dose of insulin that is too large for immediate needs.
- Rapid development of hypoglycemia in individuals with intact hypoglycemic awareness causes signs of autonomic hyperactivity, both sympathetic (tachycardia, palpitations, sweating) and parasympathetic (nausea, hunger) and may progress to convulsions and coma if untreated.
- In patients with persistent, untreated hypoglycemia, the manifestations of insulin excess may develop - confusion, weakness, bizarre behavior, coma, seizures- at which point they may not be able to procure or safely swallow glucose-containing foods.

Treatment of Hypoglycemia

- All of the manifestations of hypoglycemia are relieved by glucose administration.
- To expedite absorption, simple sugar or glucose should be given, preferably in a liquid form.
- To treat mild hypoglycemia in a patient who is conscious and able to swallow, orange juice, glucose gel, or any sugar-containing beverage or food may be given.
- If more severe hypoglycemia has produced unconsciousness, the treatment of choice is to give 20–50 mL of 50% glucose solution by intravenous infusion over a period of 2–3 minutes.
- If intravenous therapy is not available, 1 mg of glucagon injected either s.c. or i.m. will usually restore consciousness within 15 minutes to permit ingestion of sugar.
- In general, oral feeding is contraindicated in unconscious patients.
- Emergency medical services should be called for all episodes of severely impaired consciousness.

Immunopathology of Insulin Therapy

- There are two major types of immune disorders in these patients:

o Insulin Allergy

- an immediate type hypersensitivity, is a rare condition in which local or systemic urticaria results from histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies.
- In severe cases, anaphylaxis results.
- Because sensitivity is often to noninsulin protein contaminants, the highly purified and human insulins have markedly reduced the incidence of insulin allergy, especially local reactions.

o Immune Insulin Resistance

- A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligable extent develops in most insulin-treated patients.

Lipodystrophy at Injection Sites

- Injection of older insulin preparations sometimes led to atrophy of subcutaneous fatty tissue at the site of injection.
- This type of immune complication is almost never seen since the development of human insulin preparations of neutral pH.
- Hypertrophy of subcutaneous fatty tissue remains a problem, even with the purified insulins, if injected repeatedly at the same site.
- However, this may be corrected by avoidance of that specific injection site.