Drugs used for Diabetes Mellitus

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Drugs for Diabetes

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans **(β cells produce insulin**, α cells produce glucagon, and δ cells produce somatostatin).

A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious **hyperglycemia**. Left untreated, **retinopathy, nephropathy, neuropathy, and cardiovascular** complications may result.

Administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes.

INSULIN

Insulin aspart NOVOLOG
Insulin detemir LEVEMIR
Insulin glargine LANTUS
Insulin glulisine APIDRA
Insulin lispro HUMALOG
NPH insulin suspension HUMULIN N, NOVOLIN N
Regular insulin HUMULIN R, NOVOLIN R

AMYLIN ANALOG

Pramlintide SYMLIN

ORAL AGENTS

Acarbose PRECOSE
Alogliptin NESINA
Bromocriptine CYCLOSET
Canagliflozin INVOKANA
Colesevelam WELCHOL
Dapagliflozin FARXIGA
Glimepiride AMARYL
Glipizide GLUCOTROL
Glyburide DIABETA, GLYNASE PRESTAB
Linagliptin TRADJENTA
Metformin FORTAMET, GLUCOPHAGE
Miglitol GLYSET
Nateglinide STARLIX
Pioglitazone ACTOS
Repaglinide PRANDIN
Rosiglitazone AVANDIA
Saxagliptin ONGLYZA
Sitagliptin JANUVIA
Tolbutamide TOLBUTAMIDE

INCRETIN MIMETIC

DIABETES MELLITUS

The incidence of diabetes is growing rapidly in the United States and worldwide.

Diabetes is not a single disease. Rather, it 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.

	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

Comparison of type 1 and type 2 diabetes.

DIABETES MELLITUS

Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during **pregnancy**.

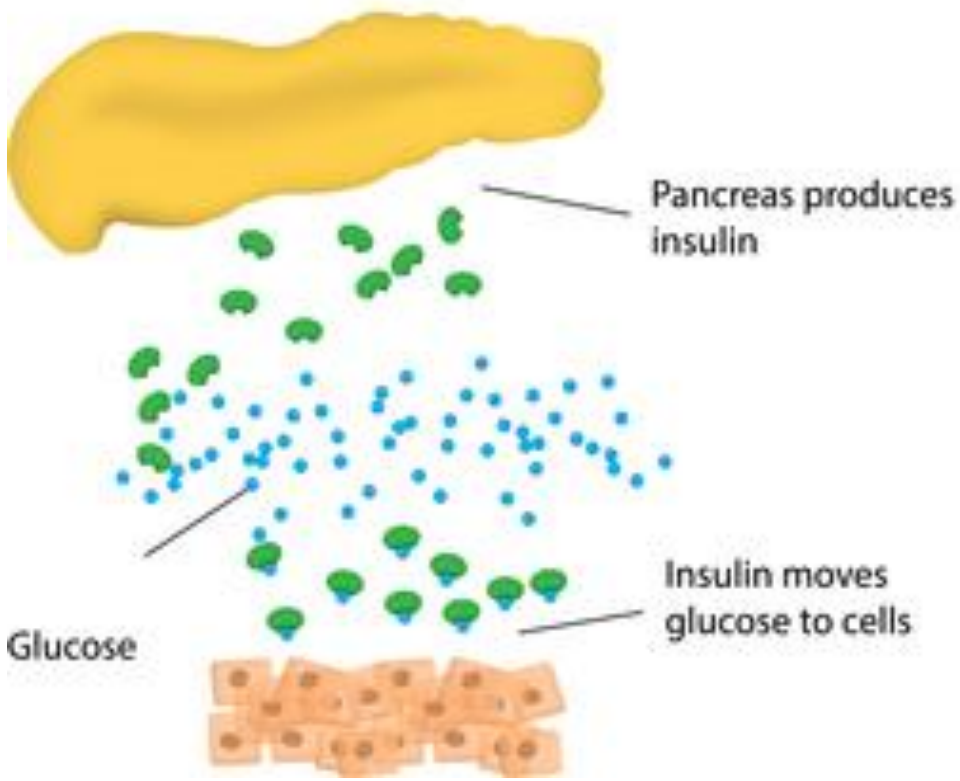
Uncontrolled gestational diabetes can lead to fetal **macrosomia** (abnormally large body) and **shoulder dystocia** (difficult delivery), as well as neonatal hypoglycemia.

Diet, exercise, and/or insulin administration are effective in this condition.

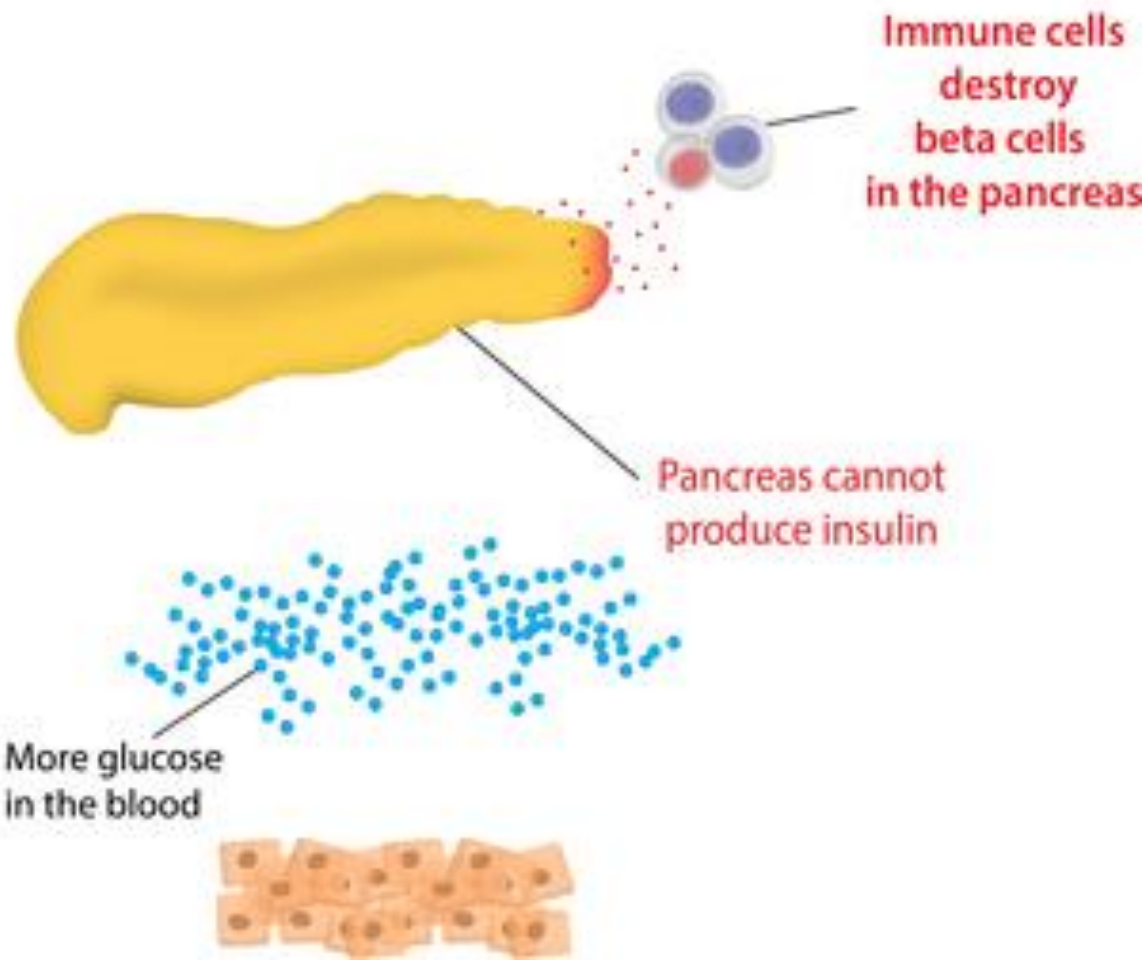
Glyburide and metformin may be reasonable alternatives to insulin therapy for gestational diabetes.

Type 1 Diabetes

Healthy



Diabetic



DIABETES MELLITUS/ A. Type 1 diabetes

Type 1 diabetes most commonly afflicts **children**, adolescents, or young adults, but some latent forms occur later in life.

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.

Without functional β cells, the **pancreas fails to respond to glucose**, and a person with type 1 diabetes 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.

DIABETES MELLITUS/ A. Type 1 diabetes/ 1. Cause of type 1 diabetes:

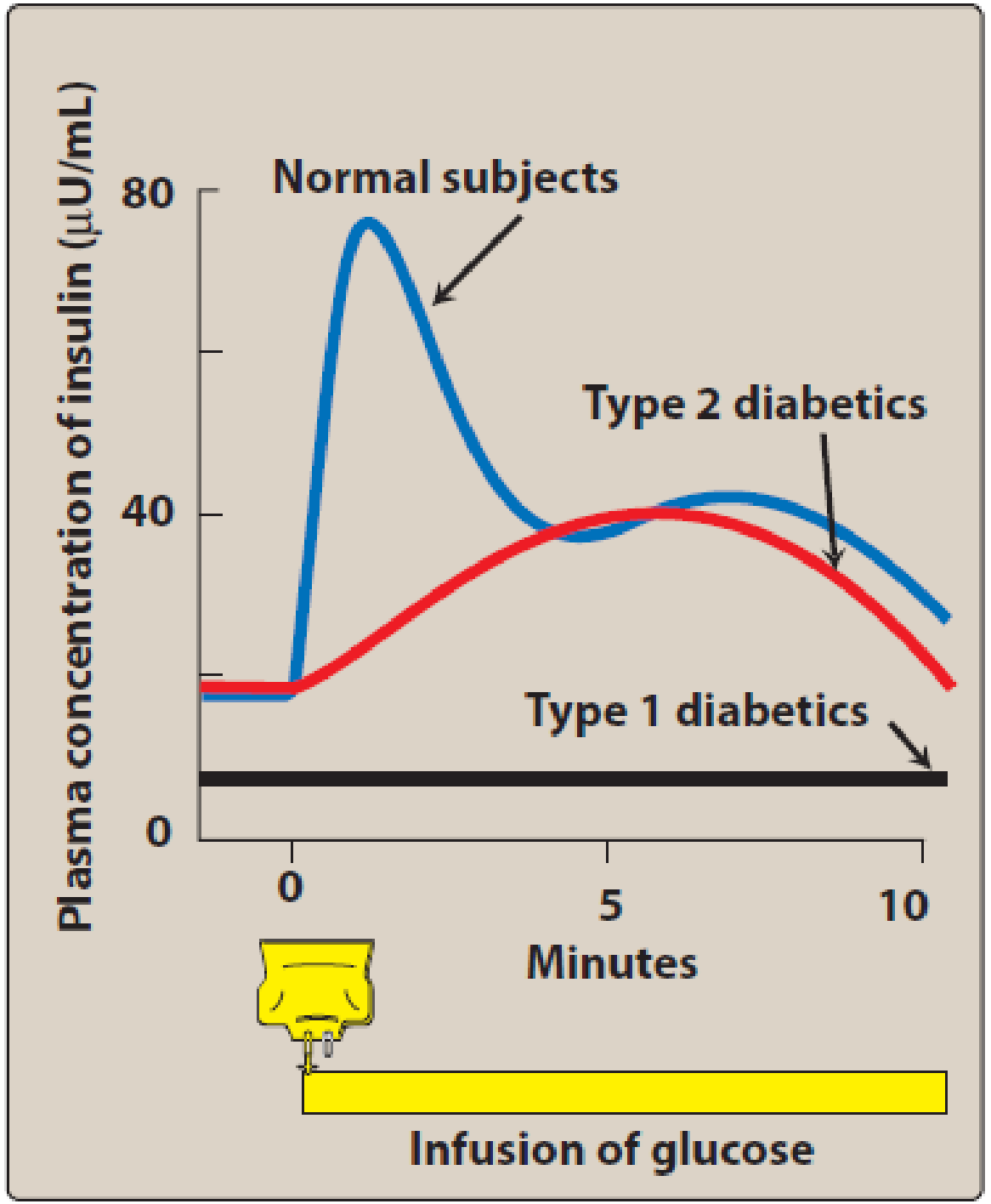
In a normal postabsorptive period, constant β-cell secretion maintains low basal levels of circulating insulin.

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.

However, without functional β cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor respond to variations in circulating glucose.



Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.

DIABETES MELLITUS/ A. Type 1 diabetes/ 2. Treatment:

A person with type 1 diabetes must rely on **exogenous insulin** to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c).

The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide swings in glucose.

The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin.

DIABETES MELLITUS/ B. Type 2 diabetes

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.

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

DIABETES MELLITUS/ B. Type 2 diabetes/ 1. 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 β-cell mass may gradually decline over time in type 2 diabetes.

In contrast to patients with type 1, those with type 2 diabetes are often **obese**.

Obesity contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.

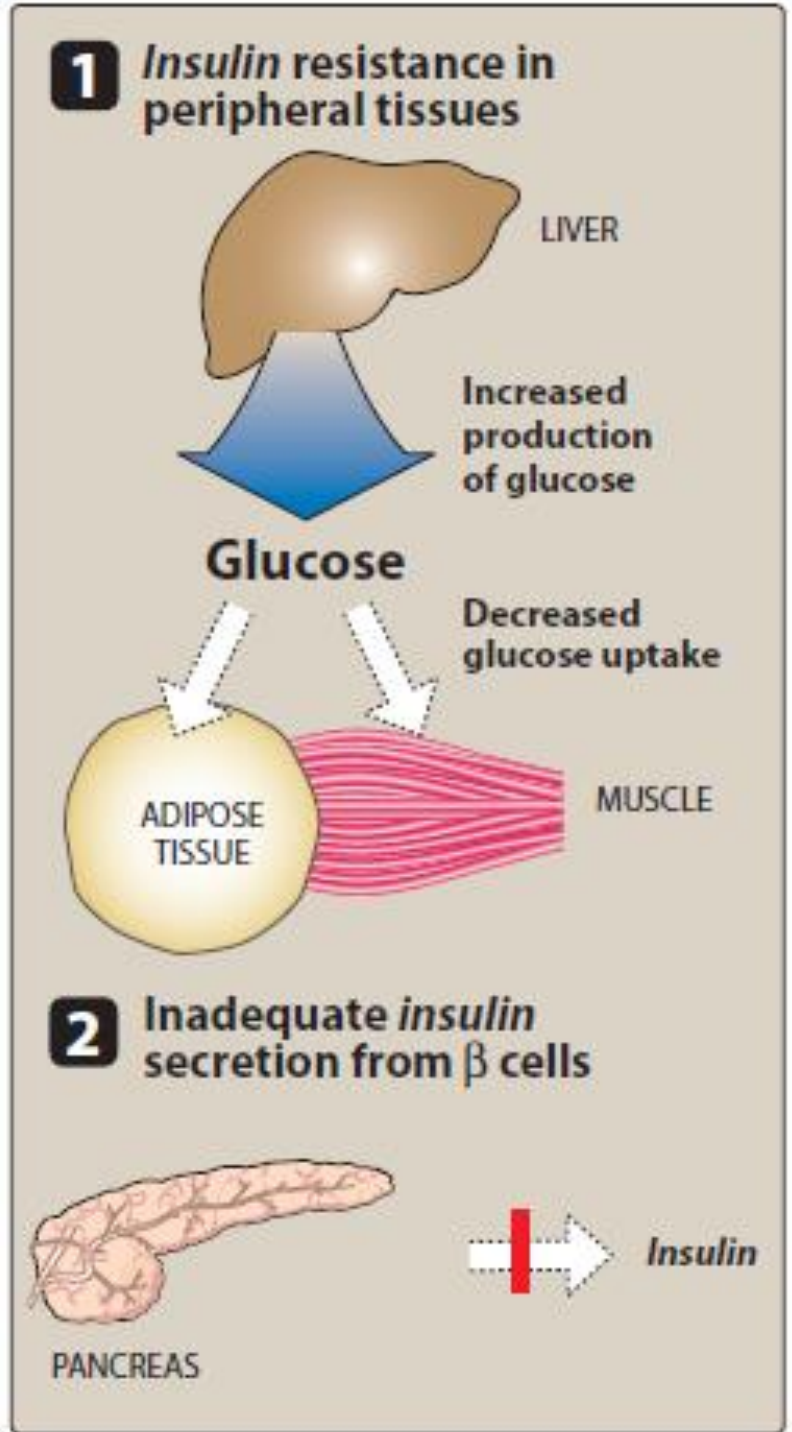
DIABETES MELLITUS/ B. Type 2 diabetes/ 2. Treatment:

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

Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes.

However, most 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.



Major factors contributing to hyperglycemia observed in type 2 diabetes.

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**, both of which are secreted by the β cells of the pancreas.

Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators.

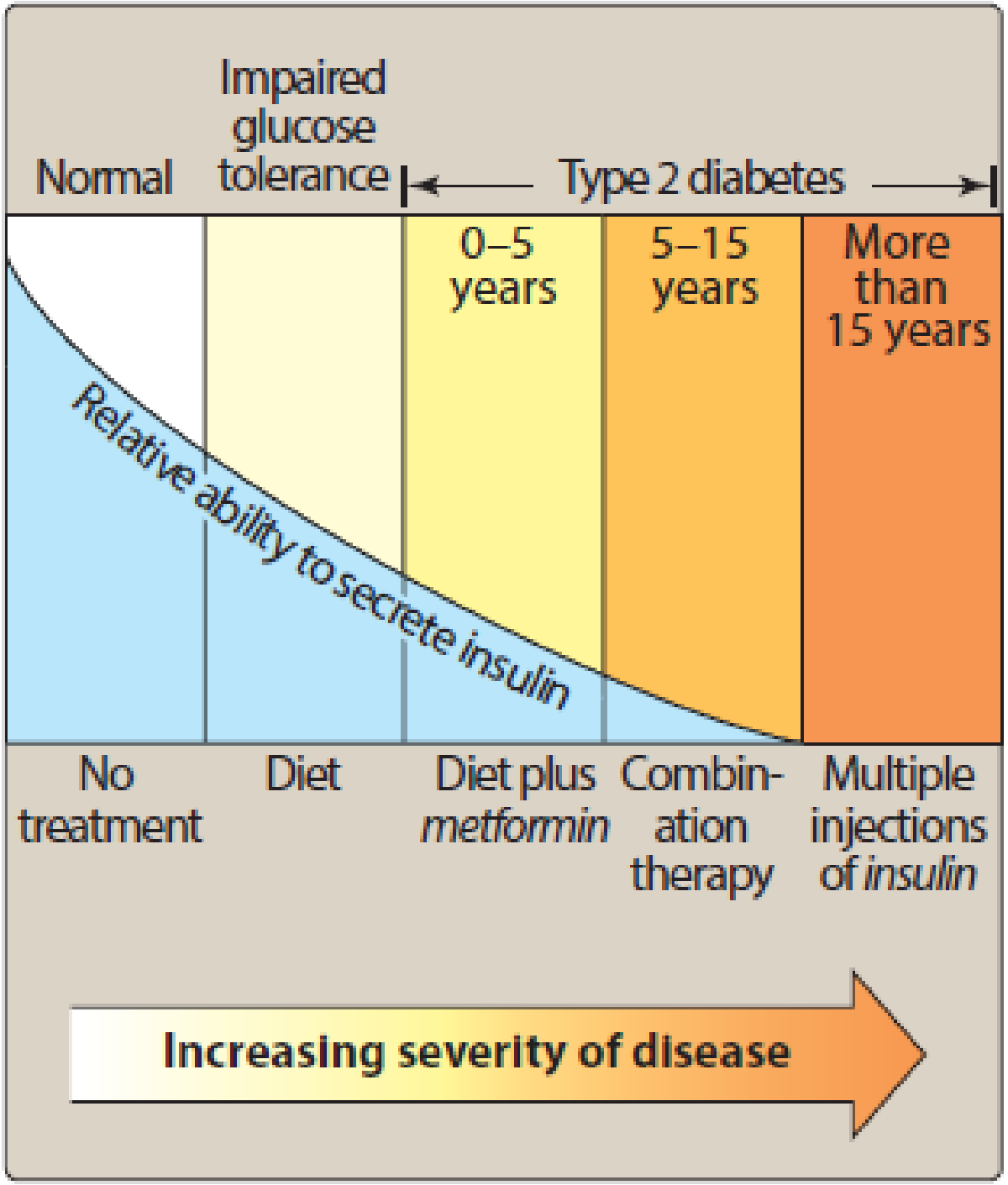
Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas.

INSULIN AND INSULIN ANALOGS

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**.



Duration of type 2 diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.

INSULIN AND INSULIN ANALOGS/ A. 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.

INSULIN AND INSULIN ANALOGS/ B. 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, aspart, and glulisine have a faster onset and shorter duration of action than regular insulin, because they do 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 gastrointestinal tract if taken orally.

Therefore, it is generally administered by subcutaneous **injection**.

INSULIN AND INSULIN ANALOGS/ B. Pharmacokinetics and fate

[Note: In a hyperglycemic emergency, regular insulin is administered intravenously (IV).]

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.

The pump is programmed to deliver a basal rate of insulin.

In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose.

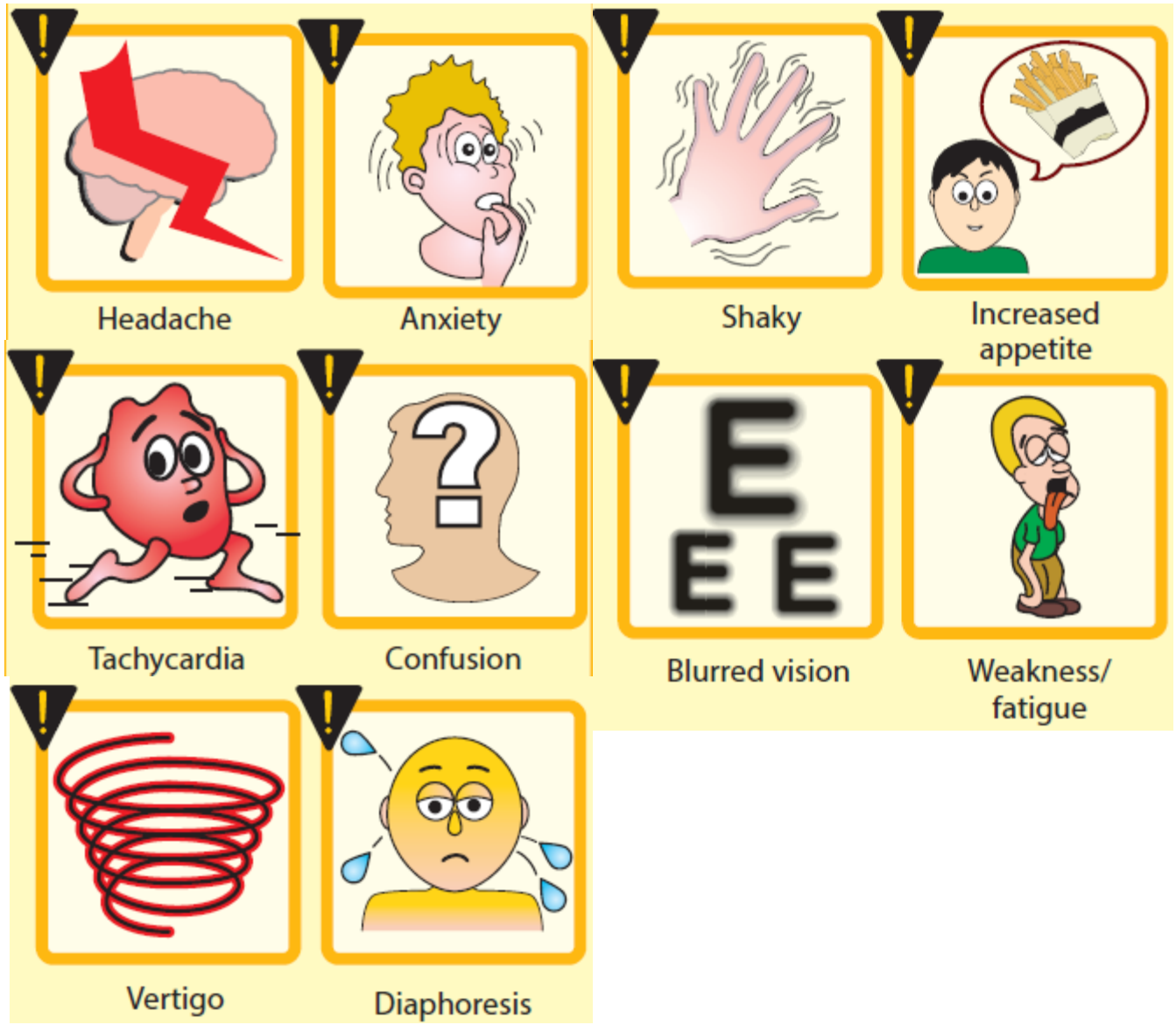
INSULIN AND INSULIN ANALOGS/ C. Adverse reactions to insulin

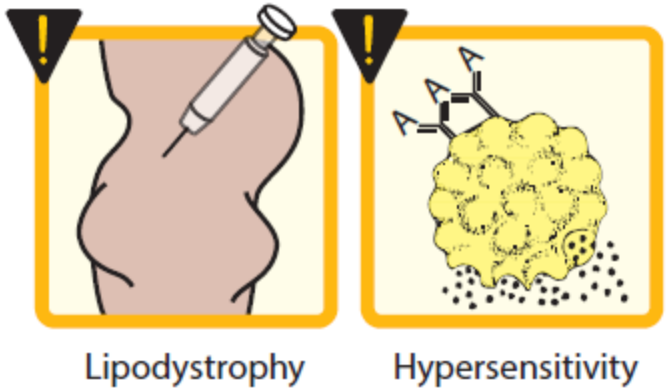
Hypoglycemia is the most serious and common adverse reaction to insulin.

Other adverse reactions 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.

Symptoms caused by hypoglycemia





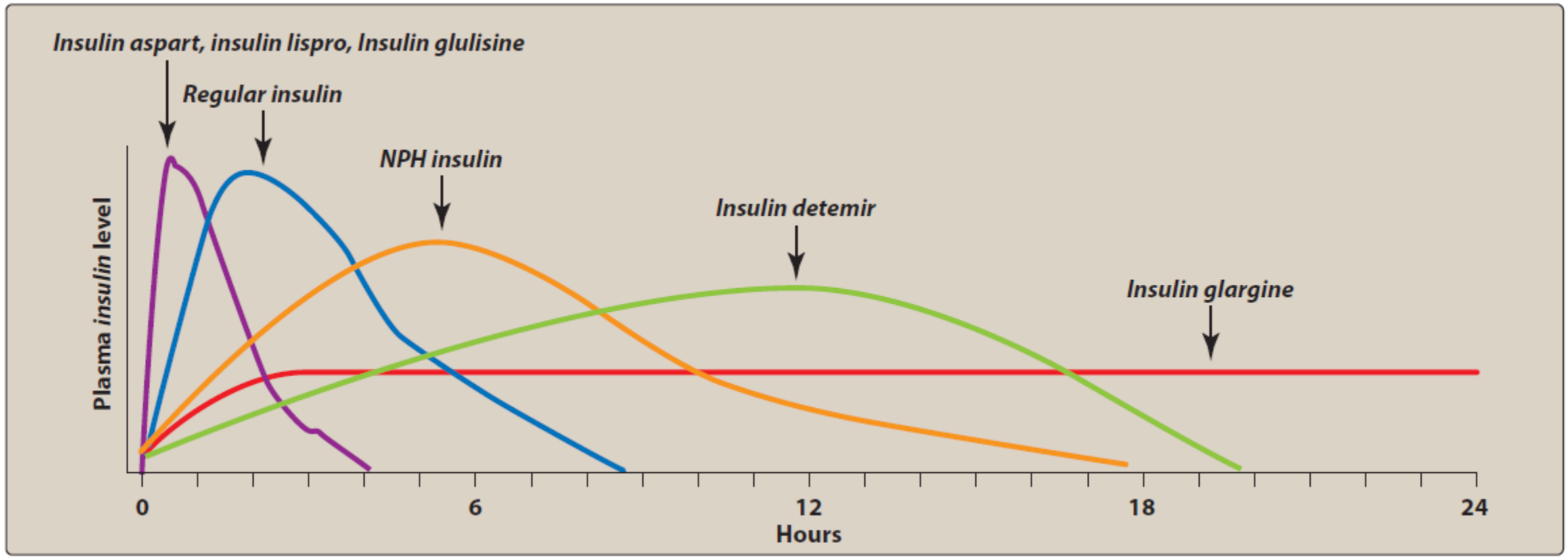
Adverse effects observed with insulin

INSULIN PREPARATIONS AND TREATMENT/

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

Figure 25.7 summarizes onset of action, timing of peak level, and duration of action for the various types of insulin.

It is important that clinicians exercise caution when adjusting insulin treatment, paying strict attention to the dose and type of insulin.


Insulin aspart, insulin lispro, Insulin glulisine
Regular insulin
NPH insulin
Insulin detemir
Insulin glargine
Plasma insulin level
0
6
12
18
24
Hours