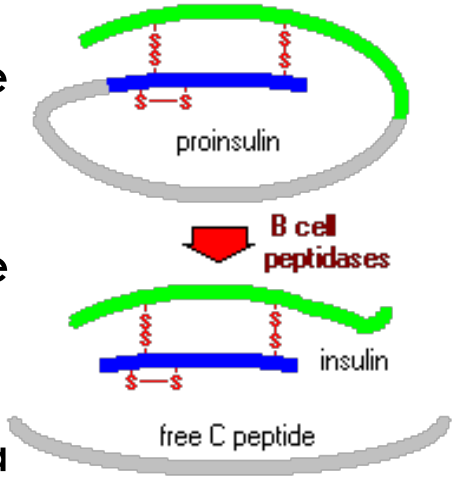
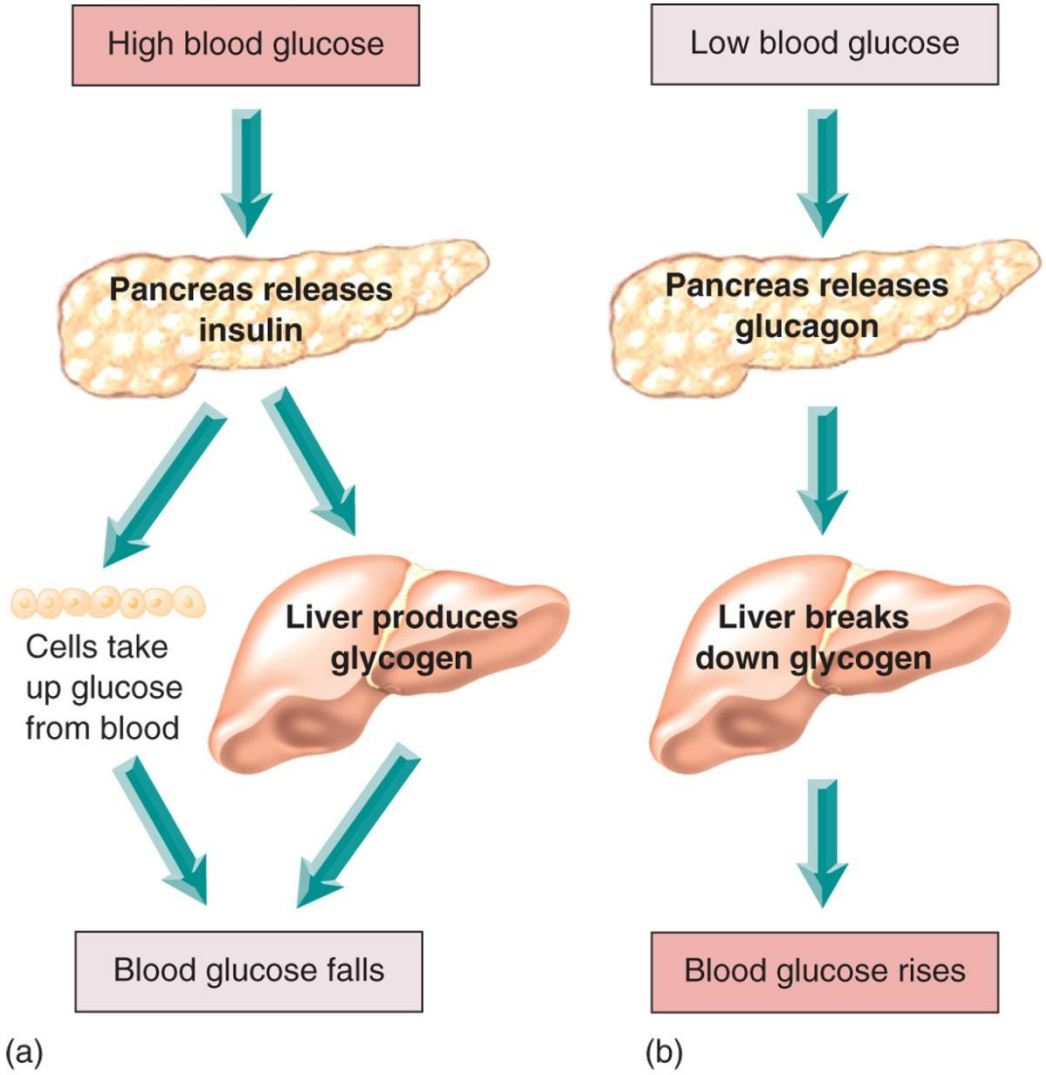
Insulin and other glucose lowering drugs

Insulin

- Insulin is secreted from β-cells of the islets of Langerhans of the pancreas
- Insulin secretion is stimulated by high plasma glucose levels and is inhibited by low plasma glucose levels
- Insulin facilitates the transport of glucose from the plasma to the liver, muscle, and adipose tissue
- Inside these tissues, glucose metabolism is used as a source of energy and to synthesize glycogen (muscle and liver) and to synthesize fats (adipose tissue)
- When starved for glucose, cells use catabolism of fats and proteins as a source of energy



Insulin, glucagon, and blood glucose



Diabetes Mellitus (DM)

DM is a group of syndromes characterized by hyperglycemia, disorder of fat, carbohydrate, and protein metabolism resulting from impaired insulin secretion, impaired insulin action or a combination of both

Types of DM:

- Insulin-dependent DM (IDDM) also known as type I

  Caused by an autoimmune reaction to insulin resulting in destruction of β cells and complete loss of insulin (10% of all diabetics)

- Non-Insulin Dependent DM (NIDDM) also known as type II

  Caused by peripheral tissue resistance to insulin actions due to decreased insulin receptor distribution or sensitivity (90% of all diabetics)

Diabetes Mellitus

- Diabetes is heterogeneous group of syndromes characterized by an elevation of blood glucose caused by a relative or absolute deficiency of insulin
- There are four clinical classifications of diabetes:
  - Type 1 diabetes (insulin dependent diabetes mellitus)
  - Type 2 diabetes (non-insulin dependent diabetes mellitus)
  - Gestational diabetes
  - Diabetes due to other causes (genetic defects or medications, etc)

	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 percent of diagnosed diabetics	90 to 95 percent 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

DM: Symptoms

Symptoms:

Hyperglycemia, glucosuria, polyurea (increase urine production due to hyperglycemia), polydipsia, polyphagia, wasting

Uncontrolled diabetes can lead to: Nephropathy, Neuropathy, Retinopathy, diabetic coma, and Diabetic Ketoacidosis (for type I)

DM: Diagnosis

Diagnosis:

The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or hemoglobin A1c [HbA1c])

Fasting Blood Glucose Test: > 125 mg/dl glucose plasma level following an overnight fasting

Oral Tolerance Test: Following a 10 hr fasting, glucose (75 grams) is given orally and plasma glucose level is measured subsequently

> 200 mg/dl at 2 hours after the oral glucose

- Normal mean blood glucose ≤ 115 mg/dL with HbA1c content ≤ 5.7

- For patients with diabetes:
  - Target mean blood glucose levels ≤ 154 mg/dL
  - HbA1c ≤ 7%

DM: Disease Management

Main objective: Glycemic control (maintain optimal plasma glucose levels and avoid hyper-or hypo-glycemia)

Glycemic control minimizes the advancement of complications e.g. retinopathy, neuropathy, and nephropathy

Glycemic control can be achieved by recombinant human insulin, oral anti-diabetics in addition to lifestyle modifications e.g. nutrition

Administration of insulin preparations or other injectable or oral glucose lowering agents can prevent morbidity and reduce mortality associated with diabetes

Insulin

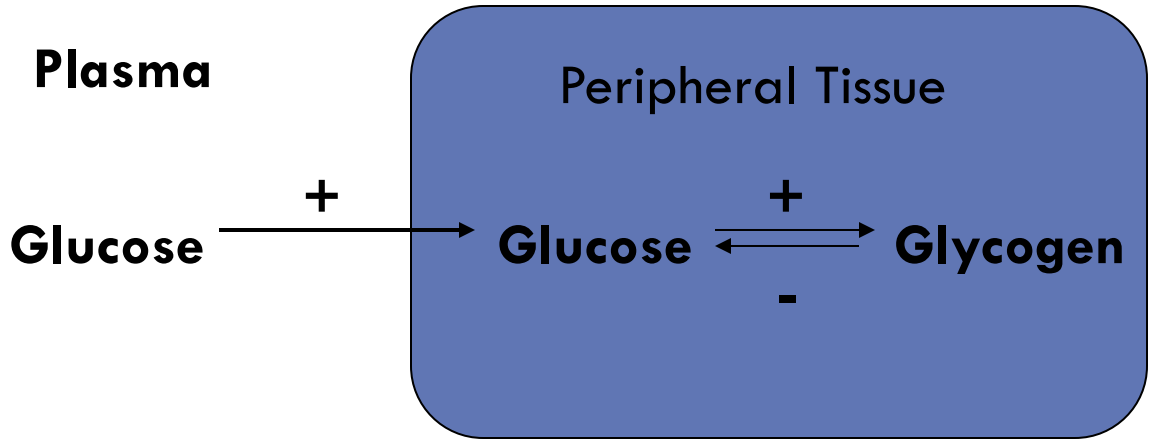
Indications:

Type I – All patients in type I have to be prescribed insulin

Type II – Many patients when other measures fail

Gestational diabetes (2% pregnancies): To avoid risks of birth defects associated with oral therapy

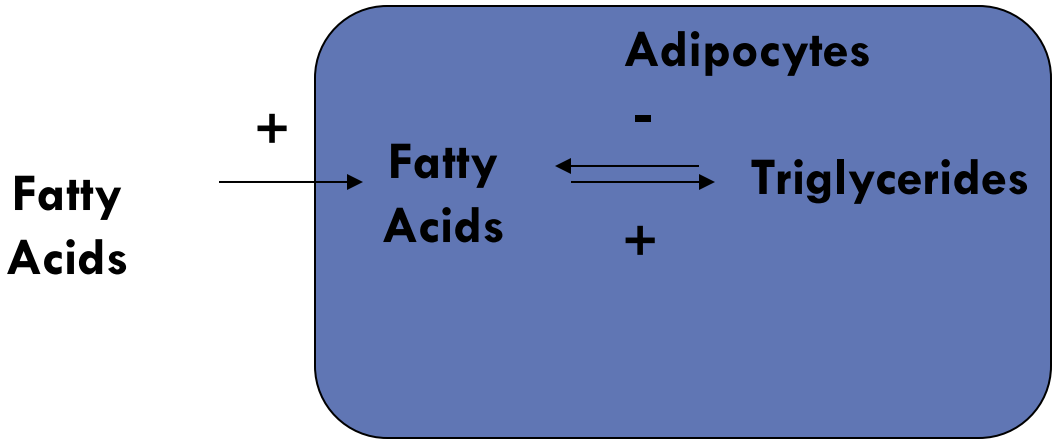
Insulin-Mechanism of Action



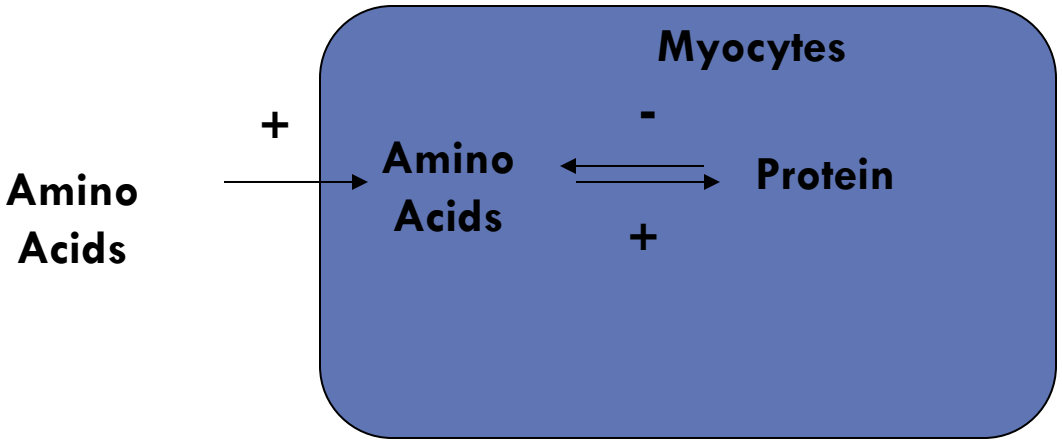
+ Insulin *stimulates* process

- Insulin *inhibits* process

Insulin-Mechanism of Action



Insulin-Mechanism of Action



Insulin

- Human insulin is produced by recombinant DNA technology
- Modifications of the amino acid sequence of human insulin have produced insulins with different PK properties
  - The 3 insulins lispro, aspart, and glulisine have a faster onset and shorter duration of action than regular insulin
  - Insulins glargine and detemir are long-acting and show prolonged flat levels following injection

Insulin preparations

- Rapid acting and short acting insulin
- Intermediate acting insulin
- Long acting insulin
- Insulin combinations

Insulin administration

- Insulin is degraded in the GIT if taken orally
- Insulin is administered by subcutaneous injection
- In a hyperglycemic emergency, regular insulin is injected IV

Rapid-acting insulin preparations

- Lispro, aspart and glulisine forms are classified as rapid-acting insulins because of their rapid onset and short duration of action

- Rapid acting insulins offer more flexible treatment regimens and may lower the risk of hypoglycemia

Rapid-acting and short-acting insulin preparations

- Regular insulin, insulin lispro, and insulin aspart are pregnancy category B

- Insulin glulisine is pregnancy category C

Regular insulin

- A short-acting
- Given subcutaneously
- Given IV in emergencies
- Rapidly lowers blood glucose

Intermediate-acting insulin

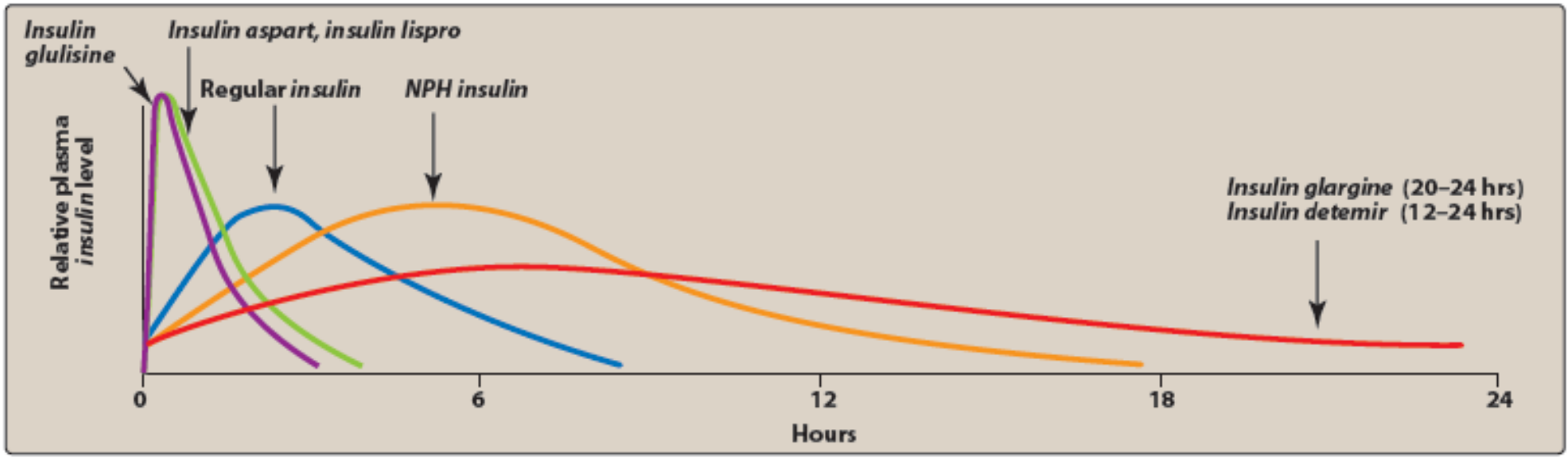
- Neutral protamine Hagedorn (NPH

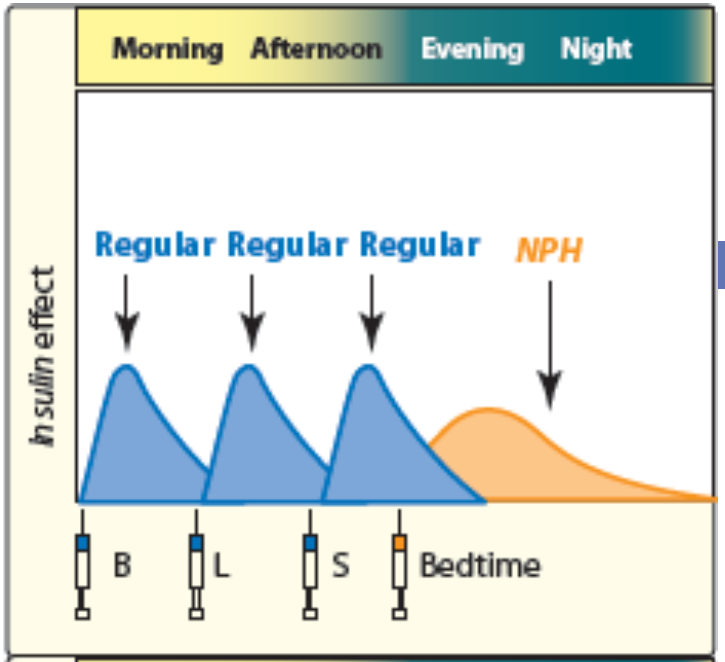
- NPH insulin should only be given subcutaneously (never IV)

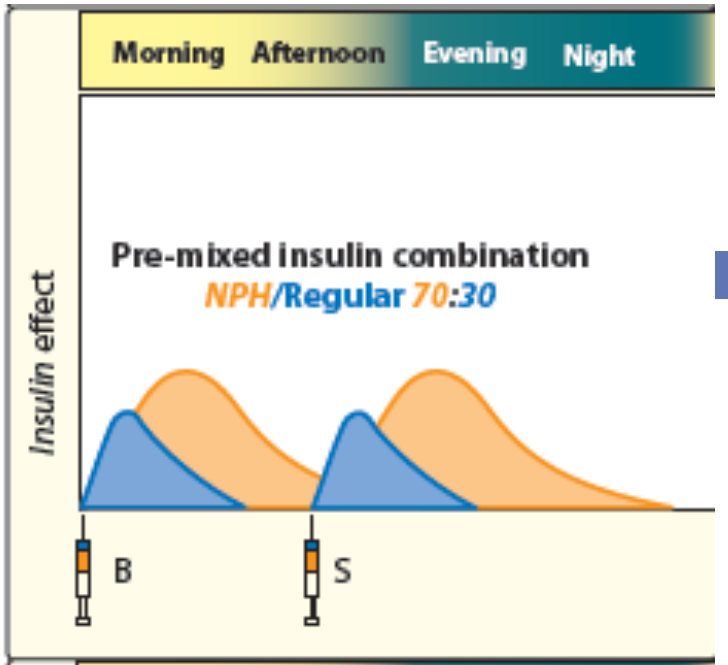
Long-acting insulin preparations

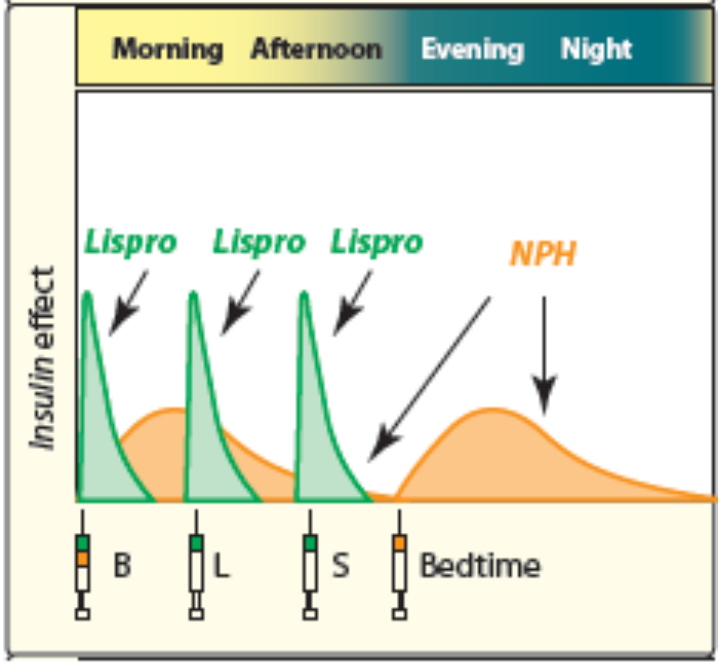
- Insulin glargine
- Insulin detemir
- Insulin detemir and insulin glargine should not be mixed in the same syringe with other insulins

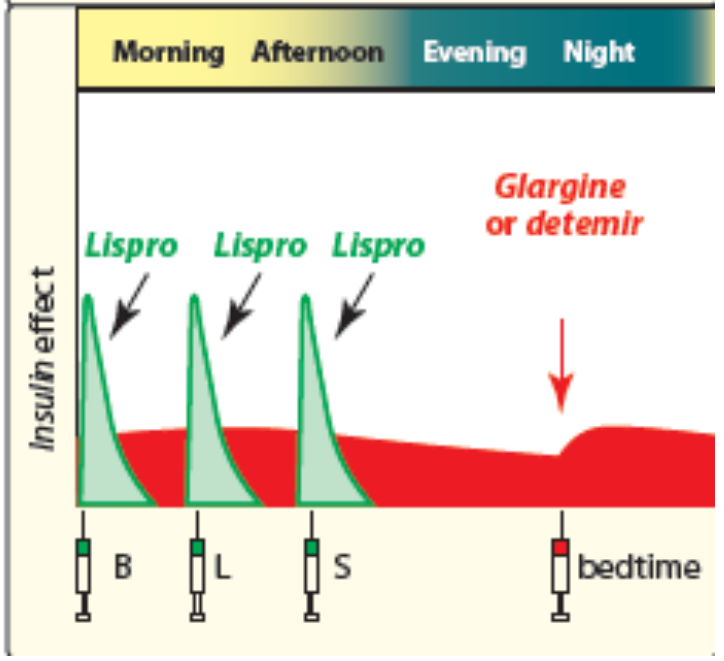
Insulin preparations




Morning
Afternoon
Evening
Night
Insulin effect
Regular
Regular
Regular
NPH
B
L
S
Bedtime


Morning
Afternoon
Evening
Night
Insulin effect
Pre-mixed insulin combination
NPH/Regular 70:30
B
S


Morning
Afternoon
Evening
Night
Insulin effect
Lispro
Lispro
Lispro
NPH
B
L
S
Bedtime


Morning
Afternoon
Evening
Night
Insulin effect
Lispro
Lispro
Lispro
Glargine
or detemir
B
L
S
bedtime

Insulin-Adverse Effects

1- Hypoglycemia

Cardiovascular: Tachycardia, palpitations

Central Nervous System: Headache, lethargy, tremors, fatigue, delirium, and sweating

2- Allergic Reactions

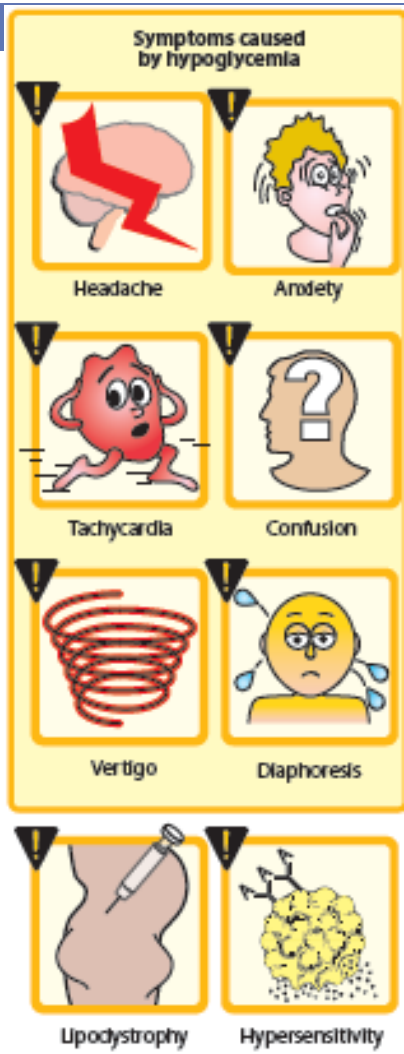
Mostly local at site of injection: erythema, redness, itchiness

3- Lipohypertrophy (local lipogenic effect of insulin)

CONTRAINDICATIONS

Allergic individuals

Hypoglycemics



Oral Antidiabetic Agents

- Insulin secretagogues
  - Sulfonylureas
  - Glinides
- Insulin sensitizers
  - Biguanides
  - Thiazolidenediones
- α-Glucosidase inhibitor

Oral glucose-lowering agents

- Insulin secretagogues: Promote insulin release from the β cells of the pancreas
  - Sulfonylureas
    - Glimepiride
    - Glipizide
    - Gllibenclamide
  - Glinides
    - Repaglinide
    - Nateglinide

Oral Anti-diabetic Agents (Type II DM)

Sulfonylureas

- Glibenclamide
- Glimepiride
- Glipizide

Mechanism of Action:

Stimulate insulin secretion from the pancreatic β cells (hypoglycemics)

Reduce insulin hepatic clearance

Enhances insulin action on peripheral tissues

Insulin sensitizers

- Insulin sensitizers improve insulin action
- Lower blood sugar by improving target-cell response to insulin without increasing pancreatic insulin secretion

- Biguanides (Metformin)

- Thiazolidenediones

Oral Anti-diabetic Agents

Biguanides (Metformin)

Mechanism of Action:

Metformin is *not* hypoglycemic but anti-hyperglycemic

Decreases hepatic glucose production

Increases insulin action on muscles and fat tissues

Thiazolidinediones (Rosiglitazone, Pioglitazone)

Mechanism of Action:

Promote insulin actions peripherally in insulin-resistant patients by increasing number of glucose transporters in target cells

Oral Anti-diabetic Agents

α-glucosidase inhibitors (Acarbose and Miglitol)

Mechanism of Action:

Inhibit α-glucosidase, an intestinal enzyme responsible for the breakdown of complex carbohydrates thus postprandial carbohydrate absorption is retarded

Oral Anti-diabetic Agents: Adverse Effects and Contraindications

Sulfonylureas: Hypoglycemia (elderly with hepatic and renal insufficiency), hemolytic anemia, cholestatic jaundice

Metformin: GI SE: Diarrhea, flatulence, nausea & vomiting – metallic taste

Rare: Lactic acidosis.

Contraindicated in patients with renal impairment, hepatic disease, and congestive heart failure

Acarbose: Mal-absorption, diarrhea, flatulence, and abdominal bloating

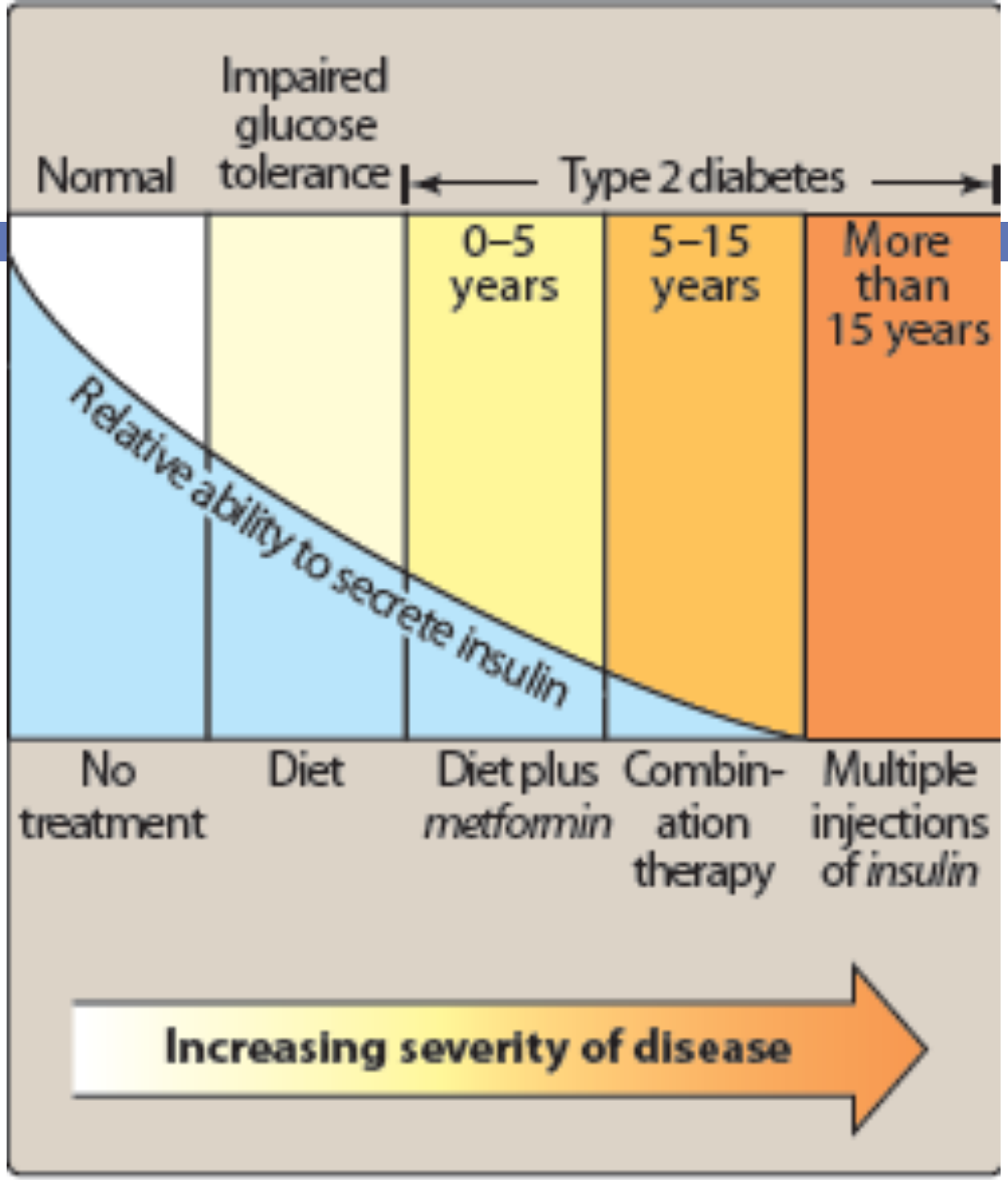
Pioglitazone: Mild anemia, moderate weight gain, and edema

General Contraindications:

Known drug allergies, active hypoglycemia, liver, kidney impairment and in pregnancy (Birth defects)

Other Agents

- Exenatide Injectable drug that belongs to class of drugs called incretin mimetics
  - Mimic effects of incretins—hormones released into blood by intestine in response to food- increase insulin – decrease gastric emptying → promotes satiety
- Pramlintide Injectable drug for type 1 and type 2; resembles human amylin
  - Hormone produced by pancreas after meals; helps body regulate blood glucose; promotes satiety and decrease glucagon secretion
  - Pramlintide may not be mixed in the same syringe with any insulin preparation


Normal
Impaired glucose tolerance
Type 2 diabetes
0–5 years
5–15 years
More than 15 years
Relative ability to secrete insulin
No treatment
Diet
Diet plus metformin
Combin-ation therapy
Multiple injections of insulin
Increasing severity of disease

Gestational diabetes

- Carbohydrate intolerance with onset or first recognition during pregnancy
  - It is important to maintain adequate glycemic control during pregnancy
  - Uncontrolled gestational diabetes can lead to fetal macrosomia (abnormally large body), shoulder dystocia (difficult delivery), and neonatal hypoglycemia
  - Diet, exercise, and or insulin administration are effective in this condition
  - Glibenclamide and metformin may be safe alternatives to insulin therapy for gestational diabetes