Drugs for Diabetes

جامعة بيرزيت
BIRZEIT UNIVERSITY

Introduction

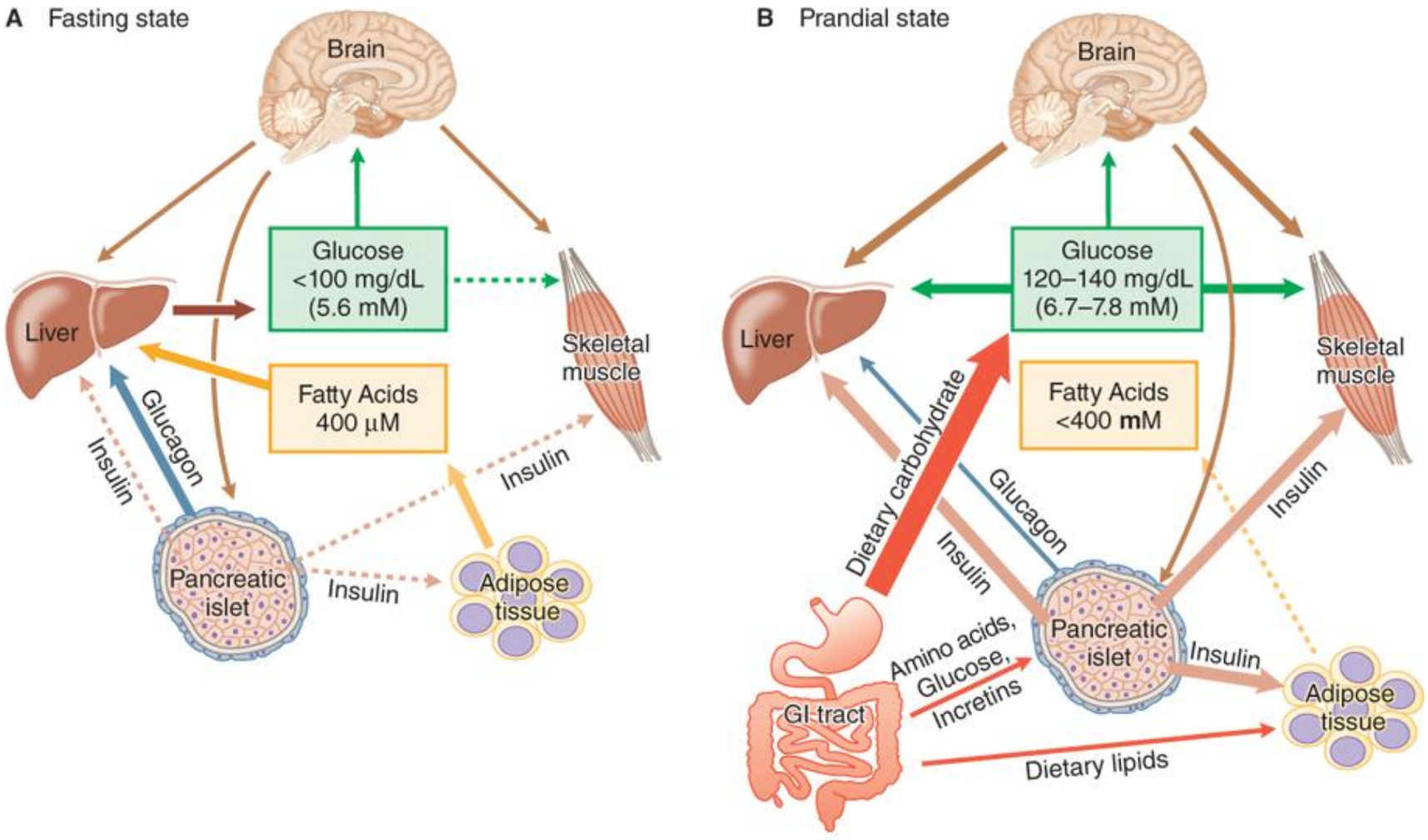
- The pancreas is both:
  - Exocrine gland that produces digestive enzymes
  - Endocrine gland that produces peptide hormones: insulin, glucagon, and somatostatin

- The peptide hormones are secreted from cells located in the islets of Langerhans
  - β cells produce insulin
  - A cells produce glucagon
  - δ cells produce somatostatin

- These hormones play an important role in regulating the metabolic activities of the body particularly the homeostasis of blood glucoses

Introduction

- Hyperinsulinemia (due for example, to an insulinoma) can cause severe hypoglycemia
- The inadequate release of insulin is commonly aggravated by an excess of glucagon
- A relative or absolute lack of insulin, such as in diabetes mellitus, can cause serious hyperglycemia
- If diabetes is left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result
- Administration of insulin preparations or other injectable or oral glucose lowering agents can prevent morbidity and reduce mortality associated with diabetes



Introduction: Diabetes

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

Introduction: Diabetes

- Gestational diabetes is defined as 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 (glyburide US) and metformin may be safe alternatives to insulin therapy for gestational diabetes

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%-10%	90%-95%
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

Figure 24.2 Comparison of type 1 and type 2 diabetes.

Type I Diabetes

- Most commonly affects individuals in puberty or early adulthood

- Some latent forms can occur later in life
- Type 1.5 LADA latent autoimmune diabetes in adults

Type I Diabetes

- Absolute deficiency of insulin caused by massive β-cell necrosis
- Loss of β-cell function is usually ascribed to autoimmune-mediated processes against the β cell
- May be triggered by an invasion of viruses or the action of chemical toxins
- Due to β-cell destruction pancreas fails to respond to glucose

Type I Diabetes

- Shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss)
- Require exogenous (injected) insulin to control hyperglycemia and maintain blood glucose concentrations as close to normal as possible
- Treatment helps in avoiding the catabolic state that results from Type I diabetes which is characterized by hyperglycemia and life-threatening ketoacidosis

Type I Diabetes

- In a normal post-absorptive period, low basal levels of circulating insulin are maintained through constant β-cell secretion which suppresses lipolysis, proteolysis, and glycogenolysis
- A burst of insulin secretion occurs within 2 minutes after a meal, in response to transient increases in circulating glucose and amino acids
- This lasts for up to 15 minutes and is followed by the postprandial secretion of insulin

Type I Diabetes

- Having non-functional β cells in T1DM can neither maintain a basal secretion level of insulin nor respond to variations in circulating fuels

- 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 HbA1c)

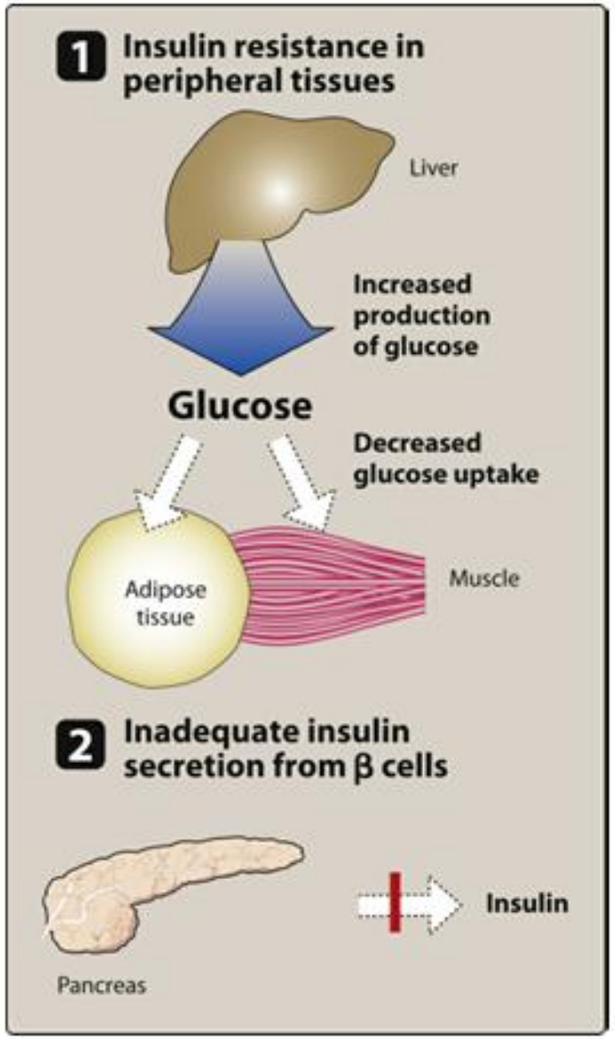
Type II Diabetes

- Most diabetic cases
- Influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes or viruses
- The metabolic alterations observed are milder than those described for type 1
- The long-term clinical consequences can be as devastating
- The pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis
- Frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous insulin

Type II Diabetes

- The pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis
- The β-cell mass may become gradually reduced in type 2 diabetes
- In contrast to patients with type 1, type 2 diabetes are often obese
- Frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous insulin

Type II Diabetes



Type II Diabetes: Treatment

- The goal in treating T2DM 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
- Most patients are dependent on pharmacologic intervention with oral glucose-lowering agents
- As the disease progresses, β-cell function declines and insulin therapy is often required

Type II Diabetes

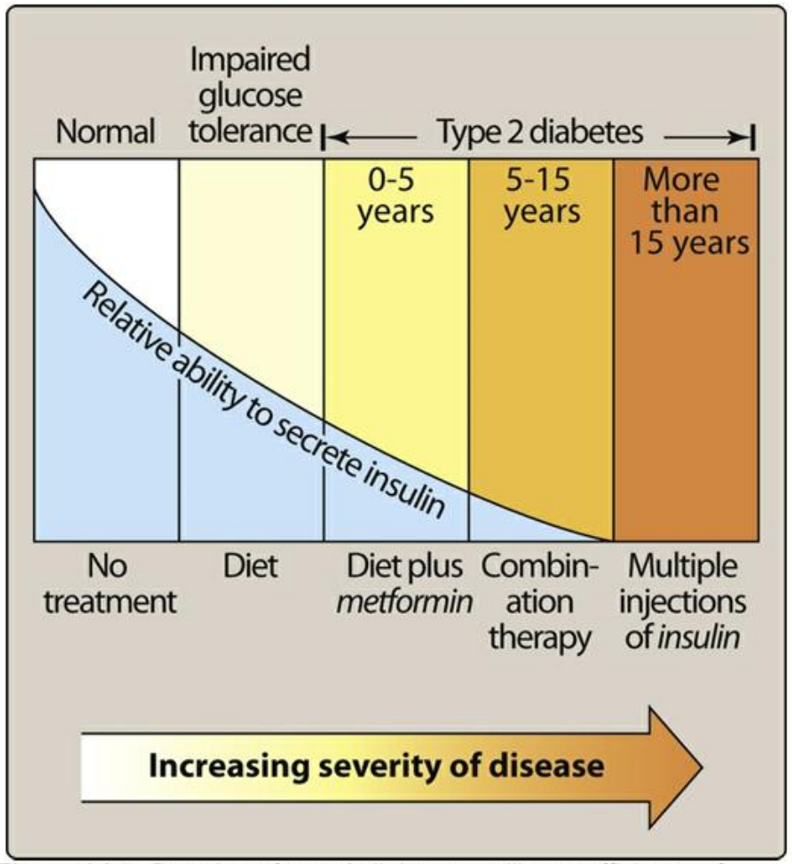


Figure 24.5 Duration of type 2 diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.Modified from M. C.Riddle . *Postgrad. Med.* 92: 89 (1992).

Diabetes diagnosis

	Normal glucose tolerance	Hyperglycemia			
		Pre-diabetes*	Diabetes Mellitus		
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control	Insulin required for survival
			Symptoms of diabetes + random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a]		
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)[b]		
HbA1C	<5.6%	5.7–6.4%	≥6.5%[c]		
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)[d]		

Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

Diabetes: treatment targets

- 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%

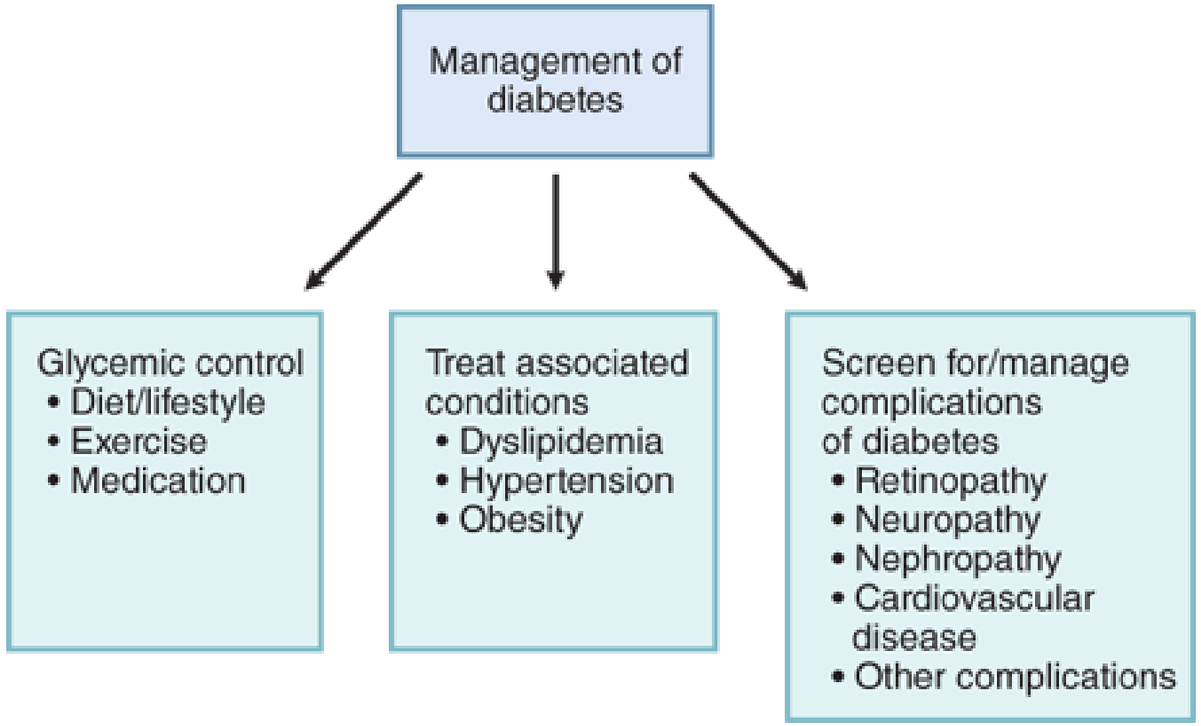
GOALS OF THERAPY FOR DIABETES IN NONPREGNANT ADULTS

INDEX	GOAL[a]
Glycemic control[b]	
A1c	<7.0%
Preprandial capillary blood glucose	4.4–7.2 mmol/L (80–130 mg/dL)
Peak postprandial capillary blood glucose	<10.0 mmol/L (<180 mg/dL)[c]
Time in range (as defined by CGM) 3.9–10.0 mmol/L (70–180 mg/dL)[d]	>70%

Diabetes: 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

Diabetes: management



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:

Insulin

- Insulin is a storage hormone:
  - It promotes anabolism
  - inhibits catabolism of carbohydrates, fatty acids and protein

- In the absence of insulin:
  - most tissues cannot use glucose
  - fats/proteins are broken down to provide energy

Insulin: MOA

- Insulin binds to insulin receptors on the plasma membrane and activates tyrosine kinase – primarily in adipose tissue, liver and skeletal muscle

Insulin: MOA

- **Liver:**
- Insulin increase the storage of glucose as glycogen in the liver
- It inserts the GLUT-2 glucose transport molecule in the cell membrane
- It inhibits gluconeogenesis – thus significantly ↓ glucose output by the liver
- It decreases protein catabolism

Insulin: MOA

- **Muscles:**
- Insulin stimulates glycogen synthesis and protein synthesis
  - Glucose transport into the cells is facilitated by GLUT-4 into the cell membrane
- Insulin inhibits the protein catabolism

Insulin: MOA

- **Adipose tissue:**
- Insulin facilitates the storage of triglyceride by:
  - Activating plasma lipoprotein lipase
  - Inhibiting intracellular lipolysis
- It increases the glucose uptake by GLUT- 4 insertion into the cell membrane

Insulin and its analogs

- Insulin is a polypeptide hormone consisting of two peptide chains connected by disulfide bonds
- Synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide
- Undergoes significant hepatic extraction
- Measurement of circulating C-peptide provides a better index of insulin levels

Insulin secretion

- Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators
- Secretion is most commonly triggered by high blood glucose
- In the pancreas, glucose is phosphorylated by glucokinase
- The products of glucose metabolism enter the mitochondrial respiratory chain and generate ATP
- The rise in ATP levels causes a block of K+ channels, leading to membrane depolarization and Ca influx
- The increase in intracellular Ca2+ causes pulsatile insulin exocytosis

- **Sulfonylureas and glinides act by inhibition of K+ channels**

Insulin secretion

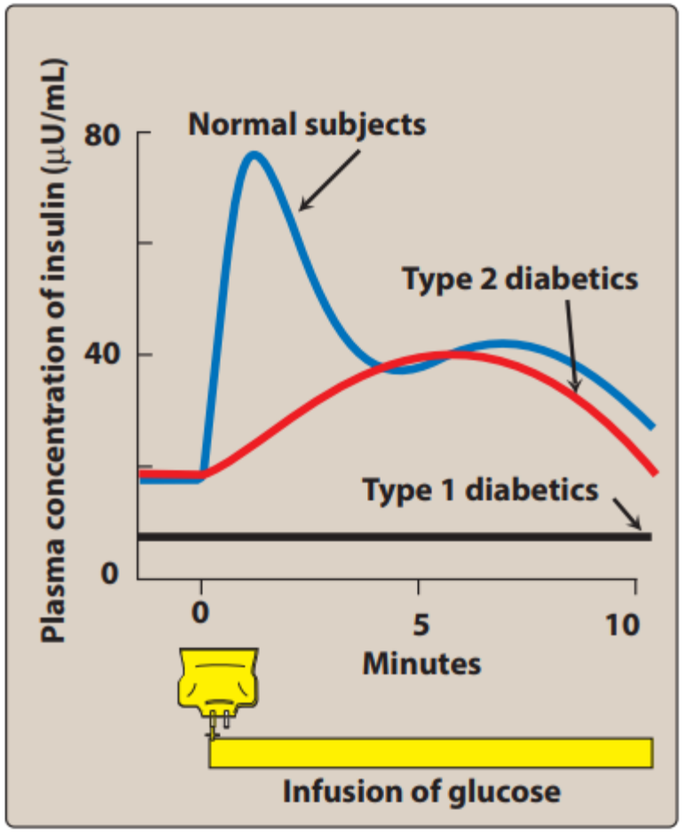


Figure 24.3
Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.

Insulin secretion

- Glucose given by injection has a weaker effect on insulin secretion than oral glucose

- When given orally, glucose stimulates production of incretin hormones by the gut, which, in turn, stimulate insulin secretion by the pancreas

Sources of insulin

- Human insulin is produced by recombinant DNA technology using E. coli or yeast altered genetically to contain the human insulin gene
- 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 and degludec are long- acting and show prolonged flat levels following injection

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
- Continuous subcutaneous insulin infusion (insulin pump) does not require multiple daily injections

Insulin administration

- Insulin preparations vary in their onset of activity and in duration of activity due to differences in their amino acids
- 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 which is found mainly in the liver and kidney

Adverse reactions to Insulin

- Symptoms of hypoglycemia in excessive dose
- Weight gain
- Lipodystrophy
- Allergic reactions
- Local injection site reactions
- Diabetics with renal insufficiency may require adjustment of the insulin dose

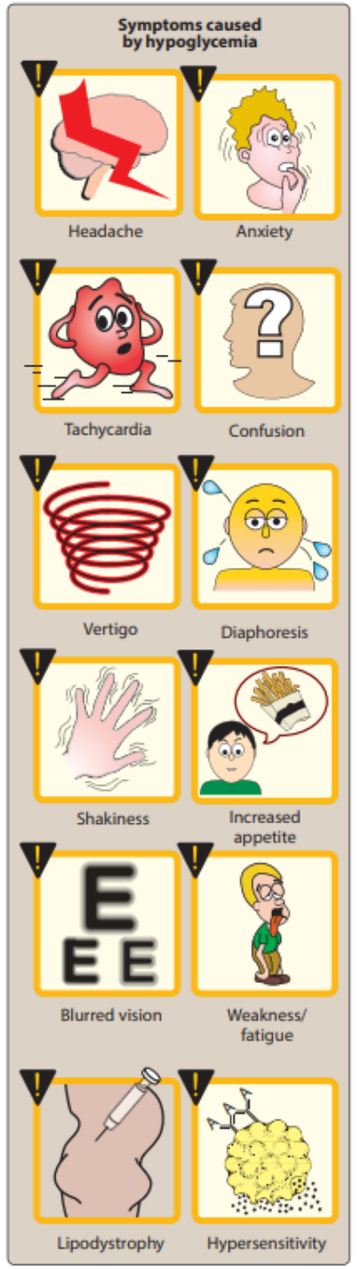


Figure 24.6
Adverse effects observed with *insulin*. [Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]

Insulin preparation and treatment

- Caution should be paid when making any change in insulin treatment and dose

Insulin preparations

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

Insulin preparations

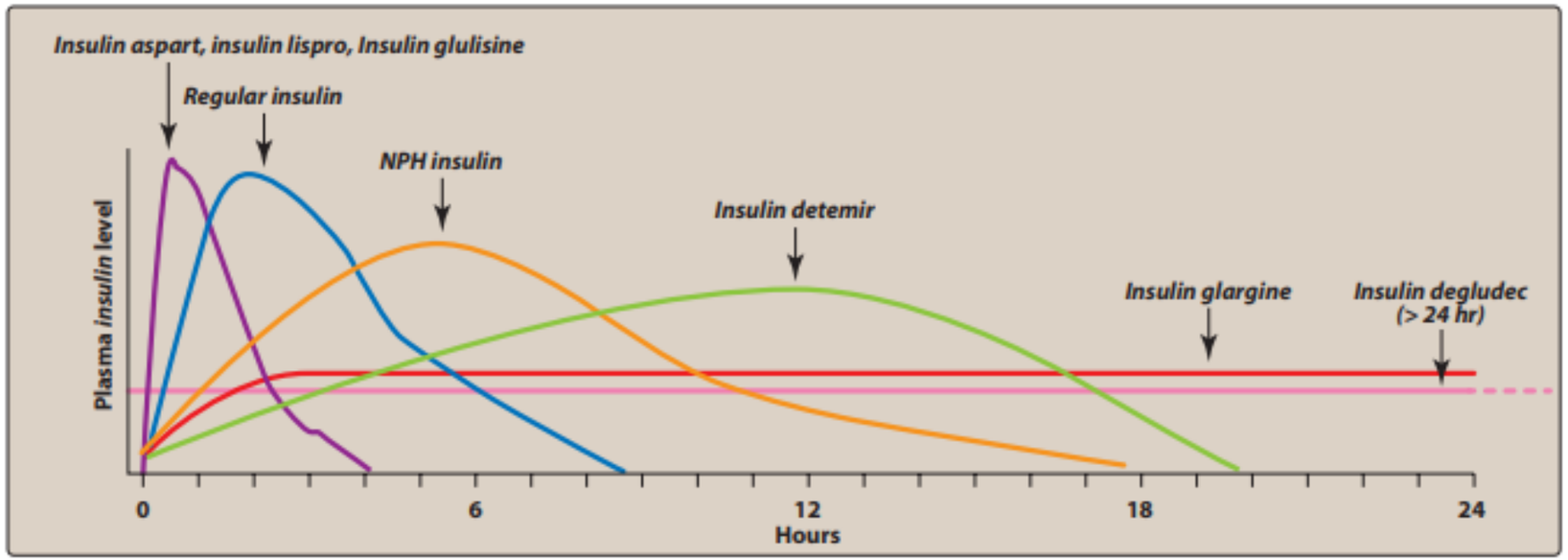


Figure 24.8

Onset and duration of action of human *insulin* and *insulin* analogs. NPH = neutral protamine Hagedorn. Modified from I. R. Hirsch. Insulin analogues. N. Engl. J. Med. 352: 174 (2005).

Rapid and short acting insulin preparations

- Include 4 preparations:
  - Regular insulin
  - Insulin lispro
  - Insulin aspart
  - Insulin glulisine

Rapid acting insulins

- 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 and short acting insulin preparations

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

- Insulin glulisine is pregnancy category C

Rapid and short acting insulin preparations

- 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 than regular insulin

Regular insulin

- A short-acting, soluble, crystalline zinc insulin
- Given subcutaneously
- Given IV in emergencies
- Rapidly lowers blood glucose

Rapid and short acting insulin preparations

- Insulin lispro is more rapidly absorbed after subcutaneous injection than regular insulin
- Insulin aspart and insulin glulisine have pharmacokinetic and pharmacodynamic properties similar to those of insulin lispro
- Administered to mimic the prandial release
- Usually not used alone but with a longer-acting insulin to ensure proper glucose control
- Administered SC

Rapid acting insulin preparations

- Insulin lispro is usually administered 15 minutes prior to a meal or immediately following a meal
- Insulin glulisine can be taken either 15 minutes before a meal or within 20 minutes after starting a meal
- Insulin aspart should be administered just prior to the meal or up to 15 minutes following the meal

Rapid and short acting insulin preparations

- All of the rapid-acting formulations are suitable for IV administration, although regular insulin is most commonly used when the IV route is needed

- Insulin lispro, insulin aspart, and insulin glulisine may also be used in external insulin pumps

Intermediate acting insulin preparations

- Neutral protamine Hagedorn (NPH) insulin suspension of crystalline zinc insulin combined at neutral pH with the positively charged polypeptide protamine
- Insulin NPH is also called insulin isophane
- Its duration of action is intermediate
- NPH insulin should only be given subcutaneously (never IV)

Intermediate acting insulin preparations

- Useful in treating all forms of diabetes except diabetic ketoacidosis and emergency hyperglycemia
- Used for basal control and is usually given along with rapid- or short-acting insulin for mealtime control
- A similar compound called neutral protamine lispro (NPL) insulin has been prepared and is used only in combination with insulin lispro (Humalog Mix ®)

Long acting insulin preparations

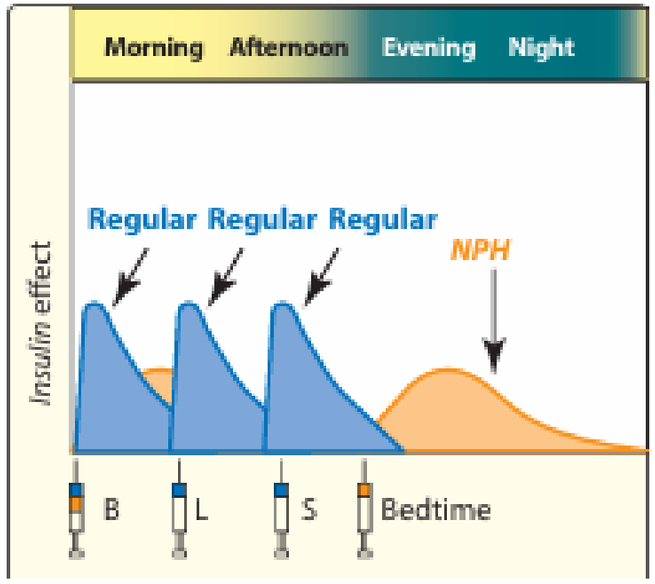
- Insulin glargine (Lantus®)
  - It is slower in onset than NPH insulin and has a flat, prolonged hypoglycemic effect with no peak
  - Given SC
- Insulin detemir
  - Has a fatty-acid side chain which enhances association to albumin
  - Slow dissociation from albumin results in long-acting properties
- Insulin Degludec
  - Insulin detemir and insulin glargine should not be mixed in the same syringe with other insulins

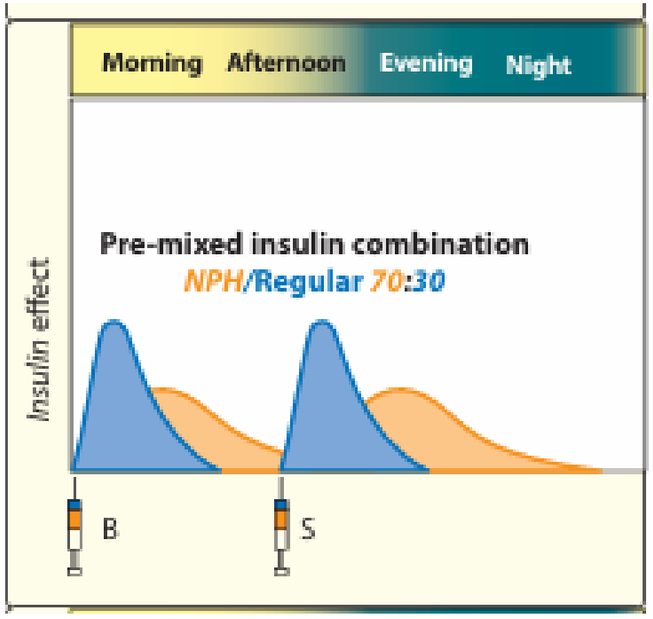
Insulin combinations

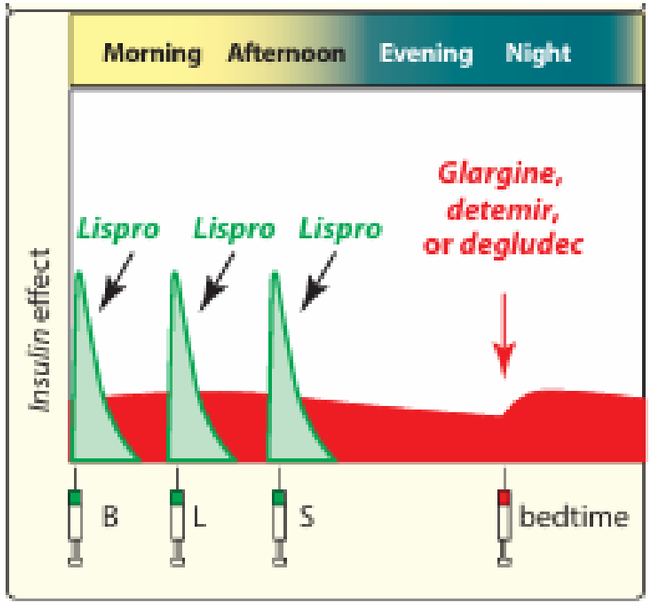
Various premixed combinations of human insulins are available

- 70% NPH insulin plus 30% regular insulin (Humulin 70/30®)
- 50% NPH insulin plus 50% regular insulin
- 75% NPL insulin plus 25% insulin lispro (Humalog Mix®)

Insulin regimens examples







Standard vs. Intensive Insulin treatment

- Standard treatment involves injection of insulin twice daily

- 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)

Standard vs. Intensive Insulin treatment

- 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%

- This is more likely to be achieved with intensive treatment

Standard vs. Intensive Insulin treatment

- The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive treatment
- Patients on intensive therapy show a significant reduction in long- term complications of diabetes as retinopathy, nephropathy, and neuropathy
- Intensive therapy has not been shown to significantly reduce the macrovascular complications of diabetes
- Intensive therapy is not recommended for patients with longstanding diabetes, significant microvascular complications, advanced age, and hypoglycemic unawareness

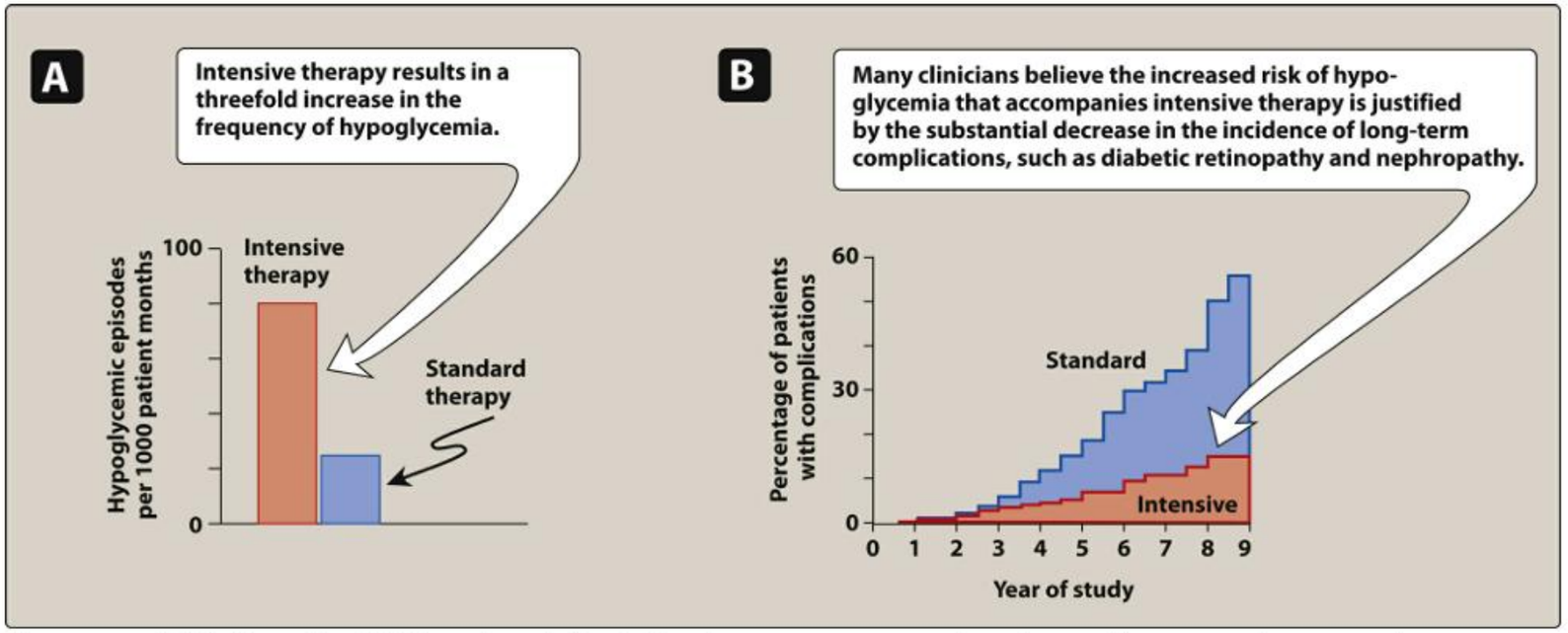


Figure 24.9 **A.** Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1 diabetes receiving intensive or standard therapy. **B.** Effect of standard and intensive care on the long-term complications of diabetes.Data from O. B.Crofford . Diabetes control and complications. *Annu. Rev. Med.* 46: 267 (1995).

Synthetic amylin analog: Pramlintide

- Used as an adjunct to mealtime insulin therapy in patients with type 1 and type 2 diabetes
- Acts as amylinomimetic, delaying gastric emptying, decreasing postprandial glucagon secretion, and improving satiety
- Administered SC and should be injected 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

Synthetic amylin analog: Pramlintide

- Adverse effects
  - Nausea
  - Anorexia
  - Vomiting

- Pramlintide should not be given to patients with diabetic gastroparesis, cresol hypersensitivity, or hypoglycemic unawareness

Incretin mimetics

- Oral glucose results in a higher secretion of insulin than occurs with IV glucose “incretin effect”
- Incretin effect is markedly reduced in type 2 diabetes
- The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 and glucose dependent insulinotropic polypeptide after a meal
- Incretin hormones are responsible for 60%-70% of postprandial insulin secretion

Incretin mimetics

- Dulaglutide (Trulicity ®)
- Semaglutide (Ozempic ®)
- Liraglutide (Saxenda®, Victoza®)
- Exenatide (Bydureon®, Byetta®)

- Injectable incretin mimetics are used for the treatment of patients with type 2 diabetes
- These agents may be used as adjunct therapy in patients who have failed to achieve adequate
- glycemic control on a sulfonylurea, metformin, a glitazone, or a combination of them

Incretin mimetics: Mechanism of action

- The incretin mimetics are analogs of GLP-1 that act as GLP-1 receptor agonists
- Improve glucose- dependent insulin secretion
- Slow gastric emptying time, decrease food intake
- Decrease postprandial glucagon secretion
- Promote β-cell proliferation
- Weight gain and postprandial hyperglycemia are reduced
- HbA1c levels decline

Incretin mimetics: Mechanism of action

- Administered subcutaneously
- Abliglutide, Dulaglutide, Semaglutide (long acting , administered once weekly)
- Liraglutide is highly protein bound and has a long half life allowing for once-daily dosing
- Exenatide should be injected twice daily within 60 minutes prior to morning and evening meals Once daily (extended release)
- Exenatide should be avoided in patients with severe renal impairment

Incretin mimetics: Adverse effects

- Nausea, vomiting, diarrhea, constipation
- Patients may form antibodies to these agents, in most cases the antibodies do not result in adverse effects
- Have been associated with pancreatitis

Oral glucose-lowering agents

- Useful in the treatment of patients who have type 2 diabetes and cannot be managed by diet alone
- Patients who have 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 combination of glucose-lowering drugs/ insulin
- Insulin is added because of the progressive decline in β cells that occurs due to the disease or aging
- Oral glucose-lowering agents should not be given to patients with type 1 diabetes

Oral glucose-lowering agents

- Insulin secretagogues
  - Sulfonylureas
  - Meglitinides
- Insulin sensitizers
  - Biguanides: Metformin
  - Thiazolidinediones
- α-Glucosidase inhibitor
- Dipeptidyl peptidase-IV inhibitors
- SGLT2 inhibitors

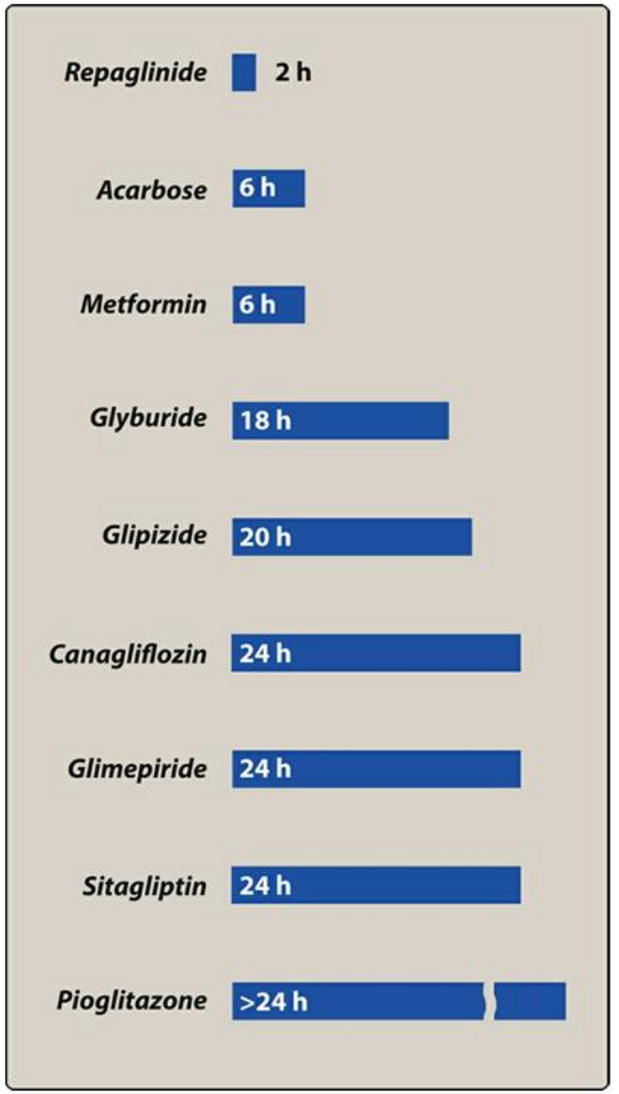


Figure 24.10 Duration of action of some oral hypoglycemic agents.

Insulin sensitizers

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

Biguanides

- **Metformin** (Glucomet®, Glucophage®, Diamet®)
- Increases glucose uptake and use by target tissues, decreasing insulin resistance
- Does not promote insulin secretion (hyperinsulinemia is not a problem)
- The risk of hypoglycemia is less than with sulfonylureas

Metformin: Mechanism of action

- Reduces hepatic glucose output by inhibiting hepatic gluconeogenesis
- Slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization
- Reduce hyperlipidemia (LDL and VLDL cholesterol concentrations fall, and HDL cholesterol rises)
- The patient commonly loses weight because of loss of appetite than with sulfonylureas

Metformin

- The ADA recommends metformin as the drug of choice for newly diagnosed type 2 diabetics
- Metformin may be used alone or in combination with one of the other agents as well as with insulin
- Hpoglycemia may occur when metformin is taken in combination with insulin

Metformin

- Metformin is well absorbed orally
- Not bound to serum proteins
- Not metabolized
- Excreted via the urine

Metformin: Adverse effects

- GI adverse effects
- Metformin is contraindicated in diabetic patients
- with renal and/or hepatic disease and in those with diabetic ketoacidosis
- Should be discontinued in cases of acute MI, exacerbation of CHF, and severe infection
- Rarely fatal lactic acidosis has occurred
- Long-term use may interfere with vitamin B12 absorption

Metformin

- 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

Thiazolidinediones (glitazones)

- Insulin sensitizers
- Insulin is required for their action
- Do not promote insulin release
- Hyperinsulinemia is not a risk
- Troglitazone (withdrawn after deaths from hepatotoxicity)
- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)

Thiazolidinediones (glitazones): MoA

- The exact mechanism by which the TZDs lower insulin resistance is unknown
- TZDs target the PPARγ
- Ligands for PPARγ regulate adipocyte production and secretion of fatty acids and glucose metabolism, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle
- Hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and elevated HbA1c levels are improved
- LDL levels are not affected by pioglitazone
- LDL levels have increased withrosiglitazone
- HDL levels increase with both drugs

Thiazolidinediones (glitazones)

- Pioglitazone and rosiglitazone can be used as monotherapy or in combination with other glucose- lowering agents or insulin
- The dose of insulin required for adequate glucose control in these circumstances may have to be lowered
- ADA recommends pioglitazone as a tier 2 alternative for patients who fail or have contraindications to metformin therapy
- Rosiglitazone is not recommended due to concerns regarding cardiac adverse effects

Thiazolidinediones (glitazones)

- Extensively bound to serum albumin
- Both undergo extensive metabolism by CYP450
- Some metabolites of pioglitazone have activity
- Elimination of pioglitazone and its metabolites is mainly in the bile
- The metabolites of rosiglitazone are primarily excreted in the urine

Thiazolidinediones (glitazones): A/Es

- Very few cases of liver toxicity with rosiglitazone or pioglitazone
- Because of deaths due to hepatotoxicity from troglitazone it is recommended that liver enzyme are periodically checked
- Weight increase can occur
- Osteopenia and increased fracture risk
- Increased risk of myocardial infarction and death from cardiovascular causes with rosiglitazone
- Headache
- Anemia
- May cause resumption of ovulation in some women who have been anovulatory
- Premenopausal women should be counseled about the need for adequate contraception while taking TZDs

Insulin secretagogues

- Insulin secretagogues: Promote insulin release from the β cells of the pancreas
- Sulfonylureas
  - Glibenclamide= Glyburide (US) (Glucocare®, Gluconil®, Declamide®, Daonil®)
  - Glimepiride (Amaryl®)
  - Glipizide(Gluco-Rite®)

- Meglitinides
  - Repaglinide (Novonorm®)
  - Nateglinide

Sulfonylureas

- Promote insulin release from the β cells of the pancreas
- The primary drugs used today are the second- generation drugs glibenclamide, glipizide, and glimepiride
- **Mechanism of action:**
  - Stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization and Ca2+ influx
  - Reduction in hepatic glucose production
  - Increase in peripheral insulin sensitivity

Sulfonylureas: Adverse effects

- Weight gain
- Hyperinsulinemia
- Hypoglycemia

- Should be used with caution in patients with hepatic or renal insufficiency, because drug accumulation may cause hypoglycemia
- Renal impairment is a particular problem in the case of agents metabolized to active compounds like glibenclamide
- Glibenclamide has minimal transfer across the placenta and may be a safe alternative to insulin therapy in pregnancy

Sulfonylureas: Drug interactions

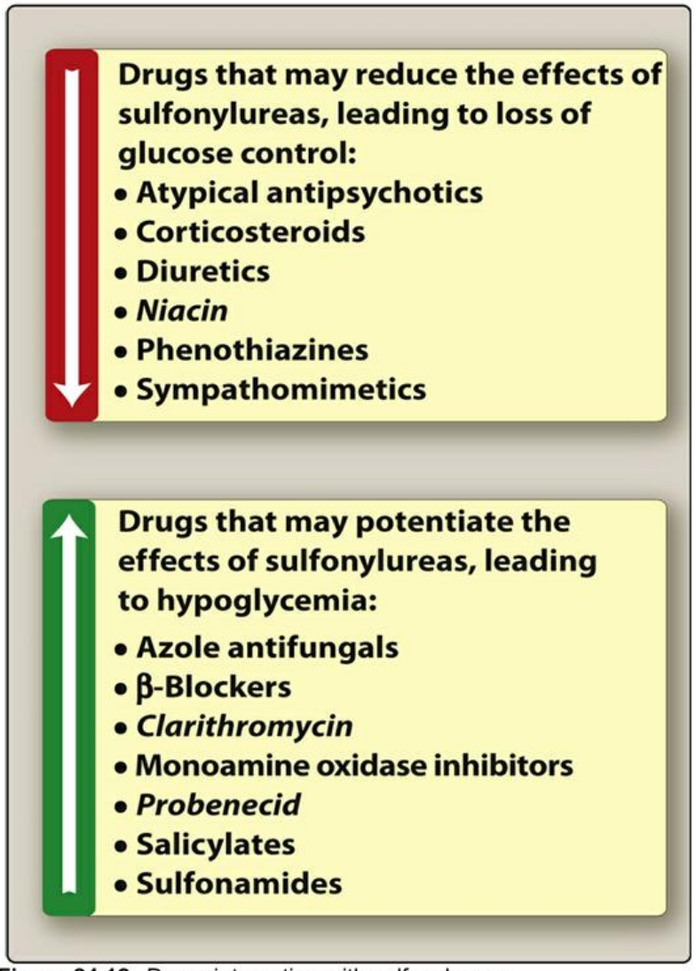


Figure 24.12 Drugs interacting with sulfonylureas.

Glinides

- Repaglinide
- Nateglinide

- **Mechanism of action:**
- Like the sulfonylureas, their action is dependent on functioning pancreatic β cells
- They bind to ATP-sensitive potassium channels leading to release of insulin
- Categorized as postprandial glucose regulators; they are particularly effective in early release of insulin after a meal

Glinides

- The glinides have a rapid onset and a short duration of action
- Combined therapy of these agents with metformin or the glitazones is better than monotherapy in improving glycemic control
- Glinides should not be used in combination with sulfonylureas (overlapping MOA)

Glinides

- Well absorbed orally after being taken 1 to 30 minutes before meals
- Metabolized to inactive products by CYP3A4
- Excreted through the bile

Glinides

- Drugs that inhibit CYP3A4 (ketoconazole, itraconazole, fluconazole, erythromycin, and clarithromycin) may enhance the glucose-lowering effect of repaglinide

- Drugs that increase levels of CYP3A4 (barbiturates, carbamazepine, and rifampin) may decrease their glucose lowering effect

- Repaglinide concurrent use with gemfibrozil is contraindicated due to reports of severe hypoglycemia

Glinides: Adverse effects

- Hypoglycemia
  - (lower incidence than sulfonylureas)
- Weight gain
  - (less than with sulfonylureas)
- Must be used with caution in patients with hepatic impairment

α-Glucosidase inhibitors

- Acarbose (Acrose®, Prandase®)
- Miglitol

- Oral drugs for the treatment of patients with type 2 diabetes

α-Glucosidase inhibitors: MoA

- Taken at the beginning of meals
- Act by delaying the digestion of carbohydrates lowering postprandial glucose levels
- Reversible inhibitors of membrane-bound α - glucosidase in the intestine
- This enzyme is responsible for hydrolysis of oligosaccharides to glucose and other sugars
- Acarbose also inhibits α-amylase, interfering with the breakdown of starch to oligosaccharides
- The postprandial rise of blood glucose is blunted

α-Glucosidase inhibitors: A/Es

- Flatulence, diarrhea, and abdominal cramping
- Patients with IBD, colonic ulceration, or intestinal obstruction should not use these drugs
- No hypoglycemia if used alone
- Hypoglycemic patient should be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs

Dipeptidyl peptidase-IV (DPP-4) inhibitors

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
- Alogliptin
- Linagliptin (Tradjenta®)

- Orally active DPP-4 inhibitors used for the treatment of patients with type 2 diabetes
- Combinations with metformin are available
  - Sitagliptin + metformin (Januet®)
  - Vildagliptin + metformin (Eucreas®)

DPP-4 inhibitors: Mechanism of action

- Inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1

- Prolonging the activity of incretin hormones results in increased insulin release in response to meals and reduction in glucagon secretion

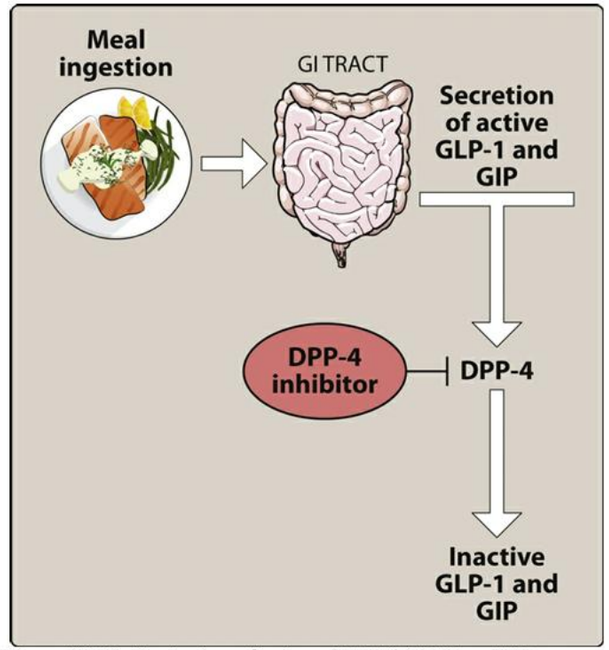


Figure 24.13 Mechanism of action of DPP-4 inhibitors.DPP-4 = dipeptidyl peptidase-4. GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1.

DPP-4 inhibitors

- DPP-4 inhibitors may be used as monotherapy or in combination with a sulfonylurea, metformin, glitazones, or insulin

- Sitagliptin and saxagliptin are excreted in urine
- Dosage adjustments for both DPP-4 inhibitors are recommended for patients with renal dysfunction

- Saxagliptin is metabolized by CYP450
- Strong inhibitors of CYP3A4/5, such as nelfinavir, atazanavir, ketoconazole, and clarithromycin, may increase levels of saxagliptin

DPP-4 inhibitors: Adverse effects

- Nasopharyngitis
- Headache
- Pancreatitis has occurred with sitagliptin
- Alogliptin and saxagliptin increase the risk of heart failure hospitalization

Sodium-glucose cotransporter 2 inhibitors

- Dapagliflozin (Farxiga®)
- Canagliflozin

- **Mechanism of action:**
- 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
- Decreases reabsorption of sodium and causes osmotic diuresis reducing systolic blood pressure

SGLT2 inhibitors

- Given once daily in the morning
- Canagliflozin should be taken before the first meal of the day
- Metabolized by glucuronidation to inactive metabolites
- Should be avoided in patients with renal dysfunction

SGLT2 inhibitors: Adverse effects

- Female genital mycotic infections urinary tract infections, and urinary frequency
- Hypotension

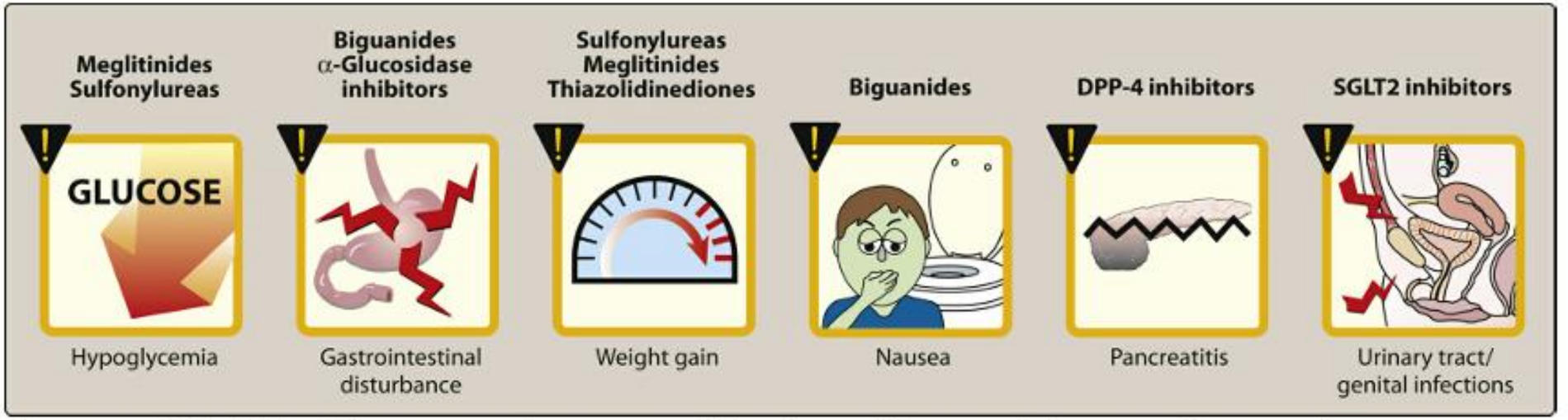


Figure 24.11 Some adverse effects with oral hypoglycemic agents.DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium–glucose cotransporter 2.

Other agents

- Bromocriptine and colesevelam produce modest reductions in HbA1c
- The mechanism of action of glucose lowering is unknown
- Indicated for type 2 diabetes
- Modest efficacy, adverse effects limit their use in clinical practice

DRUG CLASS	MECHANISM OF ACTION	RISK OF HYPOGLYCEMIA	COMMENTS
Biguanides *Metformin*	Decreases hepatic production of glucose	No	Preferred agent in type 2 diabetes. Monitor renal function and vitamin B12 levels. Avoid in severe renal impairment.
Sulfonylureas *Glimepiride* *Glipizide* *Glyburide*	Stimulates insulin secretion	Yes	Weight gain can occur. Hypoglycemia most common with this class of oral agents. Avoid *glyburide* in renal impairment.
Meglitinides *Nateglinide* *Repaglinide*	Stimulates insulin secretion	Yes (rarely)	Taken with meals. Short action with less hypoglycemia. Postprandial effect.
Thiazolidinediones *Pioglitazone* *Rosiglitazone*	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Check liver function before initiation. Avoid in liver disease or heart failure.
DPP-4 inhibitors *Alogliptin* *Linagliptin* *Sitagliptin* *Saxagliptin*	Increases glucose-dependent insulin release; decreases secretion of glucagon	No	Once-daily dosing. May be taken with or without food. Well tolerated. Risk of pancreatitis. All require renal dose adjustment, except *linagliptin*. Do not combine with GLP-1 receptor agonists
SGLT2 inhibitors *Canagliflozin* *Dapaglifozin* *Empagliflozin* *Ertugliflozin*	Increases urinary glucose excretion	No	Once-daily dosing in the morning. Risk of hypotension, genitourinary infections. Avoid in severe renal impairment. *Canagliflozin* and *empagliflozin* are approved to reduce cardiovascular mortality in patients with type 2 diabetes. *Dapagliflozin* and *empagliflozin* are also indicated for the treatment of HFrEF.
α-Glucosidase inhibitors *Acarbose* *Miglitol*	Decreases glucose absorption	No	Taken with meals. Adverse gastrointestinal effects. Not a preferred therapy. Reserve for patients unable to tolerate other agents.
GLP-1 receptor agonists *Dulaglutide* *Exenatide* *Liraglutide* *Lixisenatide* *Semaglutide*	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety	No	Injectable formulation. *Liraglutide* and *lixisenatide* are dosed once daily. *Dulaglutide* and *semaglutide* are dosed once weekly. *Semaglutide* is also available in an oral formulation. *Exenatide* is dosed twice daily and extended-release *exenatide* is dosed once weekly. *Dulaglutide, liraglutide,* and *semaglutide* are approved to reduce cardiovascular events in patients with type 2 diabetes. Weight loss may occur. Risk of pancreatitis. Contraindicated in patients with a history of medullary thyroid carcinoma.

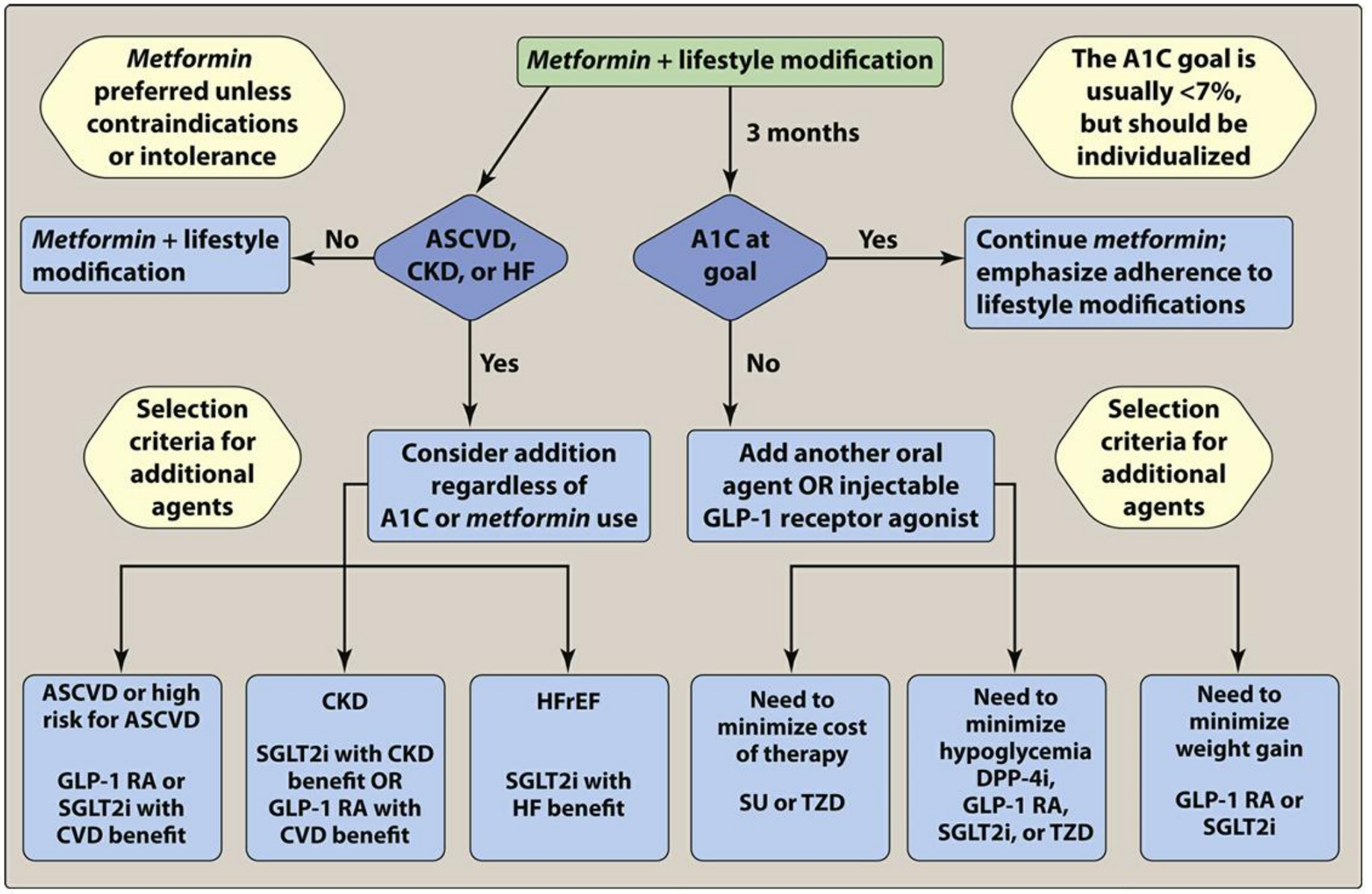


TABLE 51–6

COMPARISON OF AGENTS USED FOR TREATMENT OF DIABETES

TYPE AND AGENT	MECHANISM OF ACTION	HbA_{1c} REDUCTION (%)[a]	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS AND PRECAUTIONS
Oral					
Biguanides[c]	↓ Hepatic glucose production, ↑ insulin sensitivity, influence gut function	1–2	Weight neutral, do not cause hypoglycemia, inexpensive	Diarrhea, nausea, vitamin B_{12} deficiency, lactic acidosis	GFR <30 mL/min, CHF, radiographic contrast studies, seriously ill patients, acidosis
Dipeptidyl peptidase 4 inhibitors[c]	Prolong endogenous GLP-1 action	0.4–0.8	Do not cause hypoglycemia		↓ Dose with renal disease
α-Glucosidase inhibitors[c]	↓ GI glucose absorption	0.5–0.8	↓ Postprandial glycemia	GI flatulence, elevated liver function tests	Renal/liver insufficiency
Insulin secretagogues—sulfonylureas[c]	↑ Insulin secretion	1–2	Inexpensive	Hypoglycemia, weight gain	Renal/liver insufficiency
Insulin secretagogues—nonsulfonylureas[c]	↑ Insulin secretion	1–2	Rapid onset of action, lower postprandial glucose	Hypoglycemia, precautions for elderly and renal impairment	Renal/liver insufficiency
SGLT2 inhibitors[c] (*the gliflozins*)	↑ Renal glucose excretion	0.5–0.8	Mild weight loss and BP reduction; do not cause hypoglycemia; CV and heart failure benefit	↑ Rate of lower urinary tract and genital mycotic infections; exacerbate tendency to hyperkalemia and DKA; see text for canagliflozin	Renal insufficiency
Thiazolidinediones[c] (*the glitazones*)	↓ Insulin resistance, ↑ glucose utilization	0.5–1.2	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures in females, macular edema	CHF, liver or renal insufficiency

Parenteral					
Insulin	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	Not limited	Well-known safety/adverse effect profile from much clinical experience	Injection, weight gain, hypoglycemia	Hypoglycemia
GLP-1 receptor agonists[c,d]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	0.5–1.5	Weight loss, do not cause hypoglycemia, ↓ CV events	Injection, nausea, pancreatitis	Renal disease, agents that also slow GI motility, pancreatic disease, medullary carcinoma of thyroid
Amylin agonists[b,c]	Slow gastric emptying, ↓ glucagon	0.25–0.5	Reduce postprandial glycemia; weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
Other					
Medical nutrition therapy and physical activity[c]	↓ Insulin resistance, ↑ insulin secretion	1–3	Weight loss, improved CV health	Compliance difficult, long-term success low	
Inhaled insulin[c]	↑ Glucose utilization, ↓ hepatic glucose production, other anabolic actions	0.25–0.5	Rapid onset of action	Limited clinical experience	Pulmonary disease, smoking

Hyperglycemic emergencies

- Include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS).
- Characterized by significant elevations in blood glucose.
- Treatment includes:
  - Fluids
  - Insulin
  - Potassium
  - Bicarbonate (only in severe cases of DKA)

Agents that increase blood glucose (hyperglycemics)

Glucagon:

- Uses
- First aid in cases of severe hypoglycemia when the victim is unconscious or for other reasons cannot take glucose orally
- Treatment of overdose with beta blockers
- It has positive inotropic action and chronotropic action on the heart