Diabetes mellitus

Globally, the prevalence of diabetes for all ages is estimated to be 2.8% in 2000 and projected to increase to 4.4% by 2030.

The incidence of type 2 diabetes is now epidemic, with alarming increases in prevalence in both adults and children. Diabetes is a chronic condition caused by a relative or an absolute lack of insulin.

Its hallmark clinical characteristics are symptomatic glucose intolerance resulting in hyperglycemia and alterations in lipid and protein metabolism.

The term **gestational diabetes mellitus** (GDM) is used to describe glucose intolerance that has its onset during pregnancy.

- Approximately 5% to 10% of the diagnosed diabetic population has type 1 diabetes, which usually results from autoimmune destruction of the pancreatic β-cells.

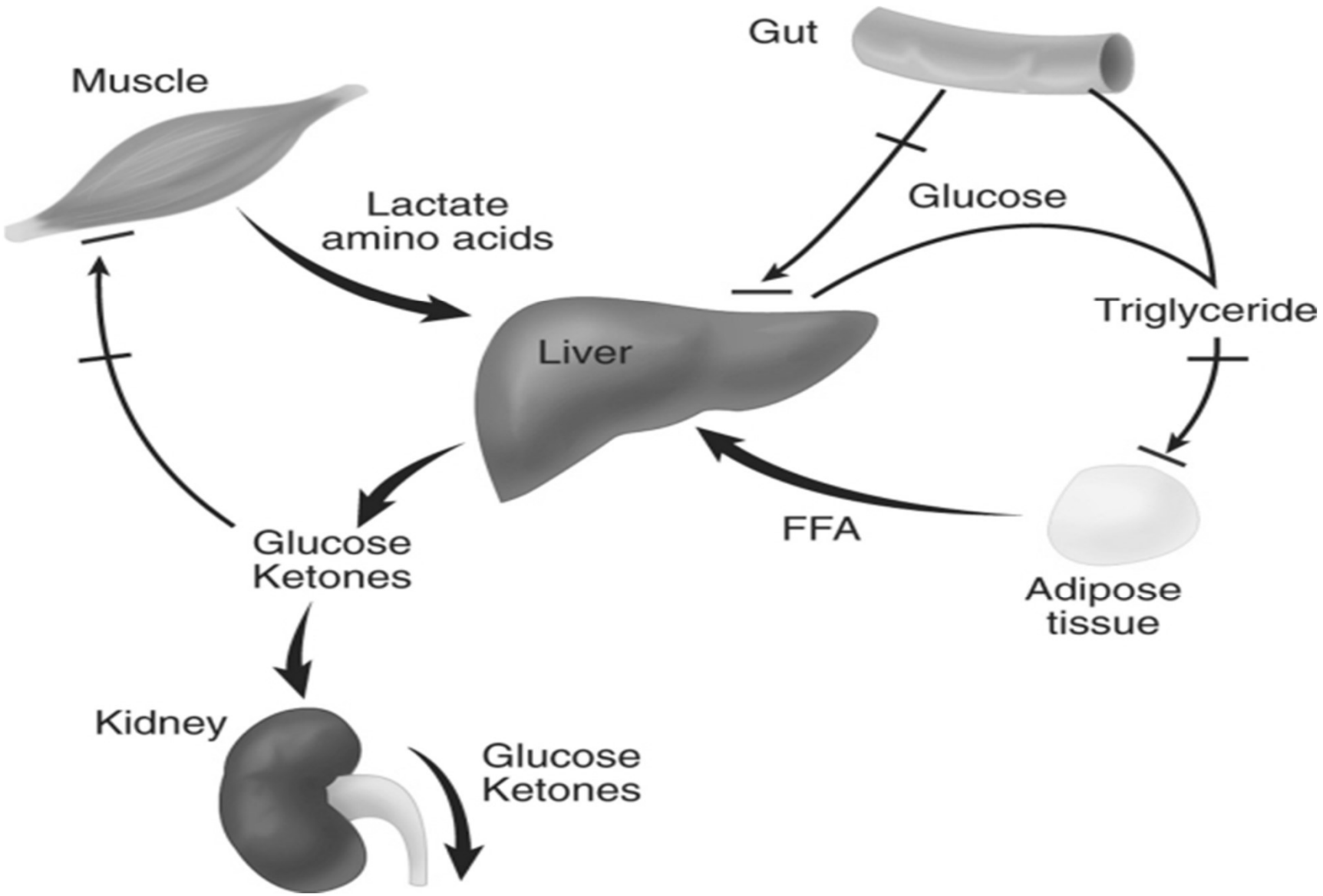
- At clinical presentation, these patients have little or no pancreatic reserve, have a tendency to develop ketoacidosis, and require exogenous insulin to sustain life.

- The incidence of autoimmune-mediated type 1 diabetes peaks during childhood and adolescence, but can occur at any age.

- A minority of patients diagnosed with type 1 diabetes, mostly of African or Asian ancestry, have no evidence of autoimmunity; the etiology is, therefore, unknown. In these individuals, the rate of pancreatic destruction seems to occur more slowly, leading to a later onset and less acute presentation.

- Most people with diabetes have type 2 diabetes, a heterogeneous disorder that is characterized by obesity, β-cell dysfunction, resistance to insulin action, and increased hepatic glucose production.

The effects of severe insulin deficiency on body fuel metabolism



Type 1 Diabetes

Pathogenesis :

The loss of insulin secretion in type 1 diabetes mellitus results from autoimmune destruction of the insulin-producing β-cells in the pancreas, which is thought to be triggered by environmental factors, such as viruses or toxins, in genetically susceptible individuals.

The capacity of normal pancreatic β-cells to secrete insulin far exceeds the normal amounts needed to control carbohydrate, fat, and protein metabolism. As a result, the clinical onset of type 1 diabetes is preceded by an extensive asymptomatic period during which β-cells are destroyed.

The earliest detectable abnormality in insulin secretion is a progressive reduction of immediate or first-phase plasma insulin response. However, this initial impairment has few detrimental effects on overall glucose homeostasis, and plasma glucose concentrations remain normal.

Most affected individuals have circulating antibodies to islet cells or to their own insulin at this stage of the disease. These represent markers of an ongoing autoimmune process that culminates in type 1 diabetes.

Fasting hyperglycemia occurs when the β-cell mass is reduced by 80% to 90%. Initially, only postprandial hyperglycemia occurs, but as insulin secretion becomes further compromised, progressive fasting hyperglycemia is seen.

Clinical Presentation:

1- polyuria with compensatory polydipsia.

2- weight loss occurs as glucose calories are lost in the urine and body fat and protein stores are broken down owing to increased rates of lipolysis and proteolysis.

3- ketonemia, ketonuria, and, ultimately, ketoacidosis.

4- Recurrent respiratory, vaginal, and other infections.

5- blurred vision secondary to osmotically induced changes in the lens of the eye.

Honeymoon Period : A period of returning back the levels of insulin and thence the normoglycemia.

Type 2 Diabetes

Pathogenesis:

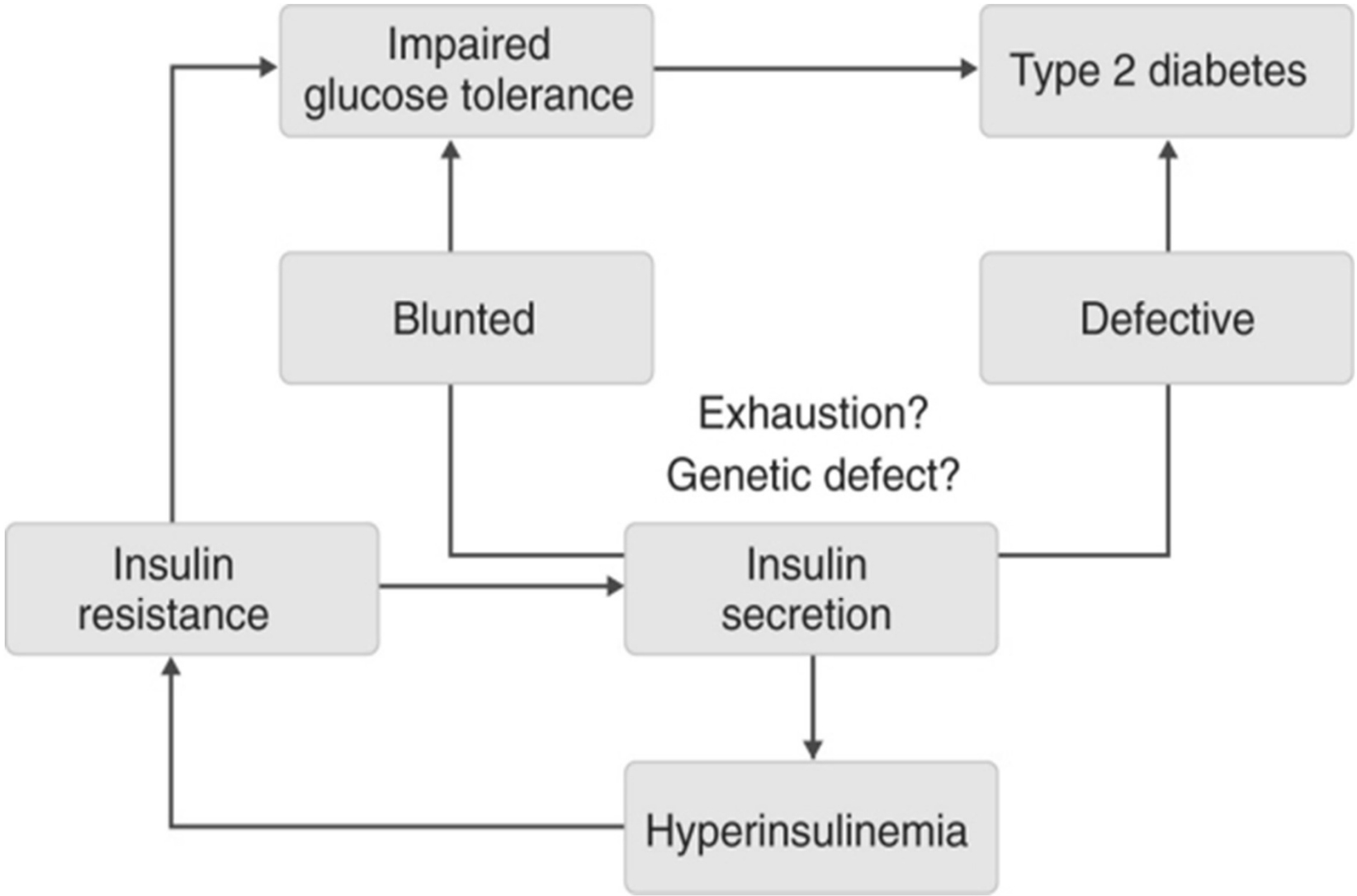
- Type 2 diabetes is characterized by impaired insulin secretion and resistance to insulin action. First- or early-phase insulin release in response to glucose often is reduced and pulsatile insulin secretion is absent, resulting in postprandial hyperglycemia.

- Over time, β-cells lose their ability to respond to elevated glucose concentrations, leading to increasing loss of glucose control. Evidence suggests that decreased peripheral glucose uptake and utilization in muscle is the primary site of insulin resistance and results in prolonged postprandial hyperglycemia.

- In patients with type 2 diabetes, altered hepatic glucose production may also contribute to or cause postprandial hyperglycemia. Obese individuals account for over 80% of patients with type 2 diabetes.

- Unlike type 1 diabetes, however, the disease generally is mild and controlled easily with diet, oral agents, or low doses of insulin (<40 units). Type 2 diabetes is associated with a variety of disorders, including hyperlipidemia, hypertension, and atherosclerosis.

A proposed sequence of events leading to the development of type 2 diabetes.



Clinical Presentation

- Type 2 diabetes is typically diagnosed incidentally during a routine physical examination or when the patient seeks attention for another complaint. people with type 2 diabetes acknowledge **fatigue**, **polyuria**, and **polydipsia**.

- There is usually no history of ketosis except in situations of unusual stress (e.g., infections, trauma). *Macrovascular* disease is also often evident at diagnosis. *Microvascular* complications at diagnosis suggest the presence of undiagnosed or subclinical diabetes for 7 to 10 years.

- Because type 2 diabetes patients retain some pancreatic reserve at the time of diagnosis, they generally can be treated with medical nutrition therapy (MNT), physical activity, and oral antidiabetic medications for several years.

- GDM affects about 7% of all pregnancies and is defined as “any carbohydrate intolerance with onset or first recognition during pregnancy.

Diagnosis

1- Classic signs and symptoms of diabetes (polyuria, polydipsia, ketonuria, and unexplained weight loss) combined with a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

2- A FPG ≥126 mg/dL (7.0 mmol/L). Fasting means no caloric intake for at least 8 hours.

3- After a standard oral glucose challenge (75 g glucose for an adult or 1.75 g/kg for a child), the venous plasma glucose concentration is ≥200 mg/dL (11.0 mmol/L) at 2 hours and >200 mg/dL (11.0 mmol/L) at least one other time during the test (0.5, 1, 1.5 hours); this is the OGTT.

- ✓ The diagnosis must be confirmed on a subsequent day by any one of these conditions in the absence of unequivocal hyperglycemia with acute metabolic complications.

- ✓ Individuals with FPG values or OGTT values that are intermediate between normal and those considered diagnostic of diabetes are considered to have “prediabetes” or IFG or IGT.

Screening for Type 2 Diabetes

- The FPG is the preferred over the OGTT as a screening test based on cost and convenience.

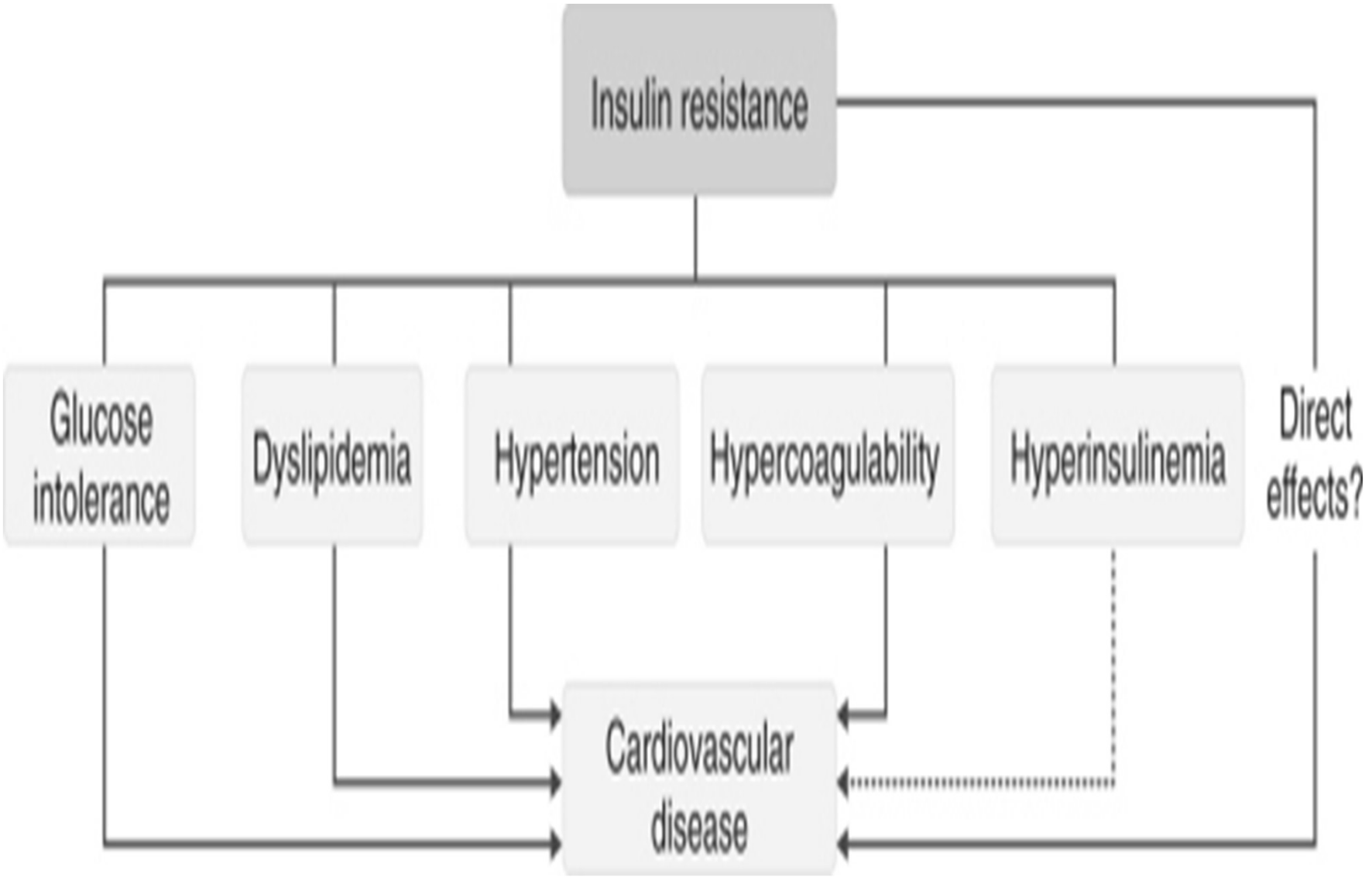
- Adults should be screened starting at age 45.

- Repeat testing should take place every 3 years. Adults may be tested at a younger age and more frequently if they are overweight (body mass index [BMI] ≥25 kg/m2) and have one or more of the risk factors.

Long-Term Complications and Their Relation to Glucose Control

- The long-term sequelae of diabetes account for most of the morbidity and mortality in the diabetic population.
- Complications are typically designated as microvascular or macrovascular in nature.
- microvascular complications are: retinopathy, nephropathy, and neuropathy.
- macrovascular disease: peripheral vascular disease, cardiovascular disease (CVD), stroke.

Metabolic syndrome and the theoretical construct of the link between insulin resistance and cardiovascular disease.



Treatment

There are three major components to the treatment of diabetes: diet, drugs (insulin and oral hypoglycemic agents, and other antihyperglycemic agents), and exercise.

Nutrition Therapy and Type 1 Diabetes Mellitus:

Adequate carbohydrates timed to match the peak action of exogenously administered mealtime insulin.

Nutrition Therapy and Type 2 Diabetes Mellitus:

For patients with type 2 diabetes, meal plans emphasize normalizing plasma glucose and lipid levels as well as maintaining a normal BP to prevent or mitigate cardiovascular morbidity.

A sustainable weight loss of 5% to 7% can be achieved within structured programs that emphasize lifestyle changes, **physical activity**, and **food intake** that modestly reduces caloric and fat intake.

Diet restriction or regulation should involve:

Carbohydrates, fat, protein, sodium salt, alcohol.

- Exercise is a key factor in the treatment of diabetes, particularly in type 2 diabetes, because obesity and inactivity contribute to the development of glucose intolerance in genetically predisposed individuals.

- **DAFNE** (Dose Adjustment For Normal Eating) in type 1 diabetes and **DESMOND** (Diabetes Education for Self Management in the Ongoing and Newly Diagnosed) in type 2 diabetes.

Pharmacologic Treatment

- Insulin, along with diet, is crucial to the survival of individuals with type 1 diabetes and plays a major role in the therapy of people with type 2 diabetes when their symptoms cannot be controlled with diet or non-insulin antidiabetic agents.

- Insulin also is used for patients with type 2 diabetes during periods of **intercurrent illness** or stress (e.g., surgery, pregnancy).

- The use of antidiabetic agents is reserved for the treatment of patients with type 2 diabetes whose symptoms cannot be controlled with diet and exercise alone.

Methods of Monitoring Glycemic Control

1- Self-monitored blood glucose (SMBG).

2- HBA1c.

3- Recently, continuous glucose monitoring (CGM) of interstitial fluid has become available for people with diabetes.

4- Urine Ketone Testing.

5- Plasma Glucose.

Insulin

Insulin is a hormone secreted from the pancreatic β-cell in response to glucose and other stimulants (e.g., amino acids, free fatty acids, gastric hormones, parasympathetic stimulation, β-adrenergic stimulation).

Immunogenicity:

immunologically mediated sequelae, such as lipodystrophy, hypersensitivity, and insulin resistance caused by "blocking" antibodies, are **now** rare.

Types of insulin:

1- Rapid-acting analogs as Insulin lispro, insulin aspart, and insulin glulisine. They are clear solutions for SC use.

2- Long-acting insulins as insulin glargine and insulin detemir. They are clear solutions intended for IV use. glargine is designed to precipitate at physiological pH and insulin detemir binds to plasma albumin.

3- Intermediate insulin {NPH(neutral protamine hagedorn or isophane)}: is a suspension in which regular insulin has been complexed with protamine to extend its action.

Two previously available insulins, **Lente and Ultralente**, were removed from the market in 2005.

NPH insulin must be mixed well before administration and should never be administered IV.

All insulin products have a neutral pH, except for insulin glargine, which has a pH of 4.0.

Pharmacokinetics:

- The rate-limiting step of insulin activity after SC administration is absorption of insulin from the injection site, which depends on the type of insulin administered, as well as a multitude of other factors.

- Exogenous insulin is degraded at both ***renal*** and ***extrarenal*** (liver and muscle) sites.

- Approximately 30% to 80% of insulin is cleared from the systemic circulation by the kidneys.

- Endogenous insulin is secreted directly into the portal circulation and is primarily cleared by the liver in nondiabetic individuals (60%).

- Insulin is filtered by glomerular capillaries, but more than 99% is reabsorbed by the proximal tubules. The insulin is then degraded in **glomerular capillary** cells and **postglomerular peritubular cells**.

- When insulin is given IV, the half-life for three compartments are 2.3 to 2.4 minutes, 14 minutes, and 133 minutes. Insulin action most closely corresponds to last compartment. Therefore, it is **unnecessary** to adjust the dose more frequently than Q 2 hr.

Treatment of Type 1 Diabetes

- The goal of diabetes management is the prevention of acute and chronic complications.

- HbA1c goal of less than 7% for patients in general and an individual goal as close to normal as possible (<6%) without significant hypoglycemia.

Basal-Bolus (Physiological) Insulin Therapy:

- *A physiological insulin regimen is designed to mimic normal insulin secretion as closely as possible.*

- Two methods have been used to achieve a similar pattern of insulin release: Insulin pump therapy & basal-bolus insulin regimens consisting of once to twice daily doses of basal insulin coupled with pre-meal doses of rapid or short-acting insulin.

Measuring and Injecting Insulin:

- ***Injection.***
- ***Rotating Injection Sites***.
- ***Agitation***.
- ***Measurement***.
- ***Reusing Insulin Syringes and Needles***.

✓ The dawn phenomenon is a rise in the blood glucose concentration that occurs between **4 and 8 AM** after a physiological nadir in the blood glucose concentration that occurs between midnight and 3 AM.

Using Insulin in Special Situations:

A) Insulin Stability:

1- Physical Changes.

2- Flocculation.

3- Temperature.

B) Other factors affecting response to insulin:

1- Exercise.

2- Sick Day Management.

3- Renal Failure.

Alternative Routes of Administration:

1- Pen Devices and Prefilled Syringes.

2- Insulin Pumps.

3- Inhaled Insulin.

Adverse Effects of Insulin:

1- Hypoglycemia:
2- Diabetic Ketoacidosis:

Treatment of Type 2 Diabetes: Antidiabetic Agents:

- Every effort to lower glucose concentrations toward normal values, control BP, and lower cholesterol is important to delay the onset or slow the progression of these complications, improve the overall quality of the patient's life, and save the health care system millions of dollars in hospitalization costs to treat these complications.

- Medical Nutrition Therapy (MNT), physical activity, and other lifestyle changes are cornerstones in treating of people with type 2 diabetes.

Biguanides

- The biguanides are described more accurately as antihyperglycemic agents. Although they lower blood glucose concentrations in people with type 2 diabetes, they do not cause hypoglycemia in nondiabetic individuals.

- metformin lowers FPG concentrations by decreasing hepatic gluconeogenesis and increasing insulin-stimulated glucose uptake by skeletal muscle and adipose tissue.

- Metformin also lowers plasma free fatty acid levels and subsequent oxidation. Metformin also slightly lowers **total cholesterol** (5%–10%) and **triglycerides** (10%–20%) and may maintain or improve high-density lipoprotein (HDL) cholesterol levels.

- Unlike the sulfonylureas, thiazolidinediones (TZDs), and insulin, weight loss rather than weight gain is more likely to occur with metformin therapy.

Adverse Effects

1- ***Gastrointestinal Effects:*** Transient side effects include diarrhea and other GI disturbances such as nausea, abdominal discomfort, metallic taste, and anorexia.

2- ***Lactic Acidosis:*** Metformin may decrease conversion of lactate to glucose (decreased gluconeogenesis) and increase lactate production in the gut and liver.

- Patients are candidates for treatment if the ClCr is above 60 mL/minute.

Nonsulfonylurea Insulin Secretagogues (Glinides)

Repaglinide (Prandin) and nateglinide (Starlix) are nonsulfonylurea insulin secretagogues (i.e., they stimulate insulin secretion).

These agents close the adenosine triphosphate (ATP)-sensitive potassium channels in the β-cell, which leads to cell membrane depolarization, an influx of Ca2+, and secretion of insulin.

Adverse Effects:

1- Mild hypoglycemia. **2-** weight gain.

Sulfonylureas

- Sulfonylureas stimulate the release of insulin from pancreatic β-cells and enhance β-cell sensitivity to glucose.

- Sulfonylureas can normalize hepatic glucose production and partially reverse insulin resistance in the peripheral tissues of people with type 2 diabetes.

- The duration of hypoglycemic activity is related to the half-life of these compounds only in very general terms and may correlate poorly in some cases.

Adverse Effects

1- hypoglycemia.

2- weight gain.

3- GI symptoms (nausea, fullness, bloating that can be relieved if taken with meals).

4- A disulfiram (Antabuse-like) reaction occurs when patients take certain oral sulfonylurea drugs(chlorpropamide) and drink ethanol.

- Chlorpropamide, and to a much lesser extent, tolbutamide, may enhance the release of antidiuretic hormone centrally, enhance the effect of antidiuretic hormone on the kidney, and override the inhibitory effects of water loading on antidiuretic hormone release, resulting in syndrome of inappropriate antidiuretic hormone secretion.

Thiazolidinediones

- The TZDs are often referred to as insulin sensitizers. TZDs bind to and activate a nuclear receptor (peroxisome proliferator-activated receptor-γ [PPAR-γ]), which is expressed in many insulin-sensitive tissues, including adipose, skeletal muscle, and liver tissue. PPAR-γ regulates transcription of genes that influence glucose and lipid metabolism.

Adverse Effects

1- ***Hepatotoxicity.***

2- ***Hematologic Effects:*** *TZD therapy may result in small decreases in hemoglobin and hematocrit and, infrequently, anemia.*

3- ***Weight Gain.***

4- ***Vascular and Cardiovascular Effects:*** Increases in plasma volume and peripheral edema (4%–6%), possibly caused by an increased endothelial cell permeability. The incidence of peripheral edema is greatly increased when TZDs are used in combination with insulin.

Glucosidase Inhibitors

- ✓ The α-glucosidase inhibitors reversibly inhibit glucosidases present in the brush-border of the mucosa of the small intestine.

- ✓ These enzymes break down complex polysaccharides and disaccharides into glucose and other absorbable monosaccharides. Enzyme inhibition delays carbohydrate digestion and subsequent glucose absorption.

Adverse Effects

1- Gastrointestinal Effects: Flatulence, diarrhea, and abdominal pain.

2- Elevated Liver Function Tests.

Dipeptidyl Peptidase-4 Inhibitors (sitagliptin):

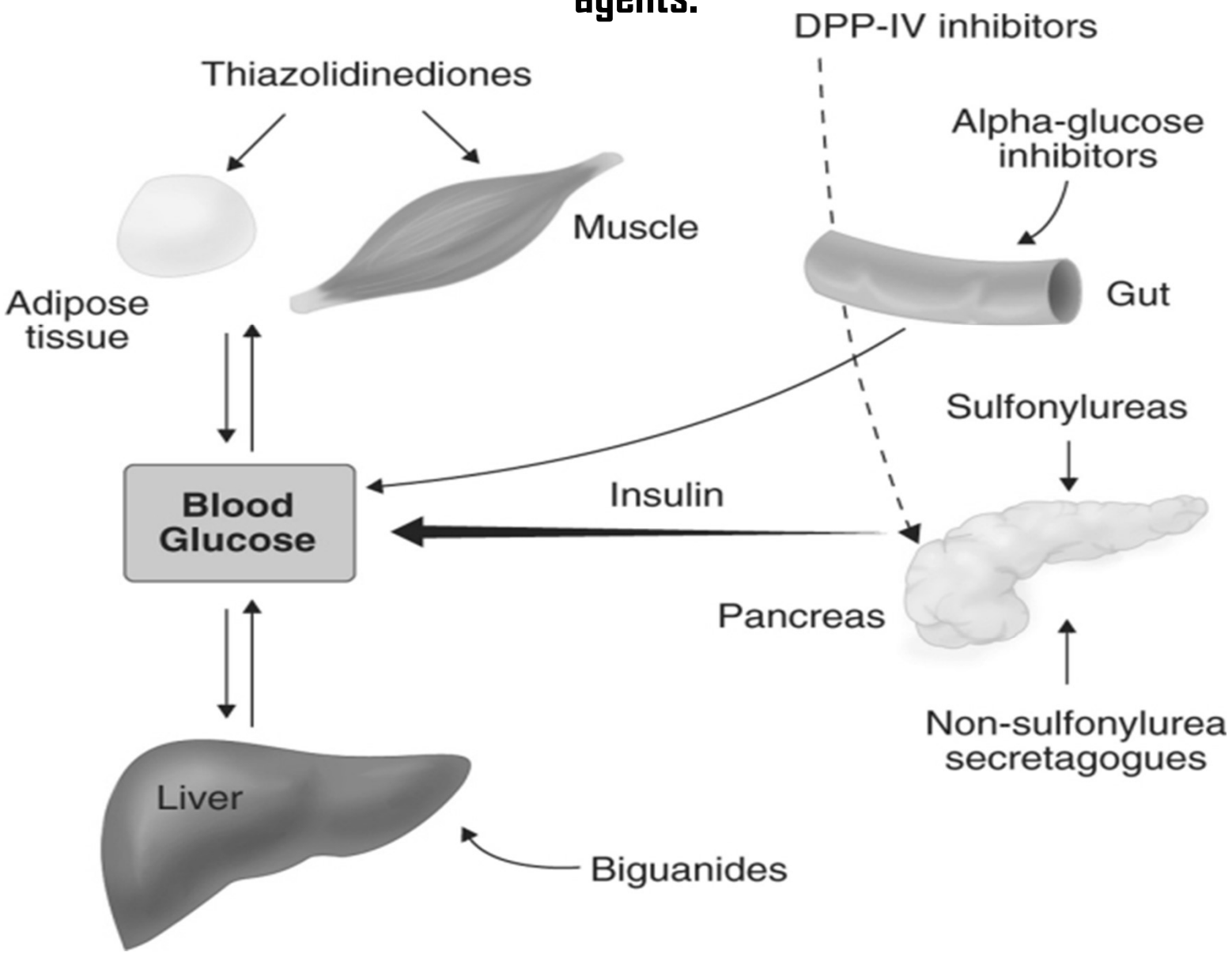
- The DDP-4 inhibitors inhibit the degradation of GIP and GLP-1 upon entering the GI vasculature, thus increasing the effects of these endogenous incretins on first-phase insulin secretion and glucagon inhibition.

- Both sitagliptin and vildagliptin reduce DPP-4 activity by 80%, with some inhibition maintained for up to 24 hours after an oral dose.

- The most commonly reported side effects with sitagliptin and vildagliptin in clinical trials include increased risk of infection [nasopharyngitis, upper respiratory tract infection].

Drug	Main route of elimination	Elimination half-life (h)	Duration of action (h)	Daily dose range	Doses per day
Sulphonylureas					
First generation					
Tolbutamide	Hepatic	4–24	6–10	0.5–2 g	1–3
Chlorpropamide	Hepatic (80%) Renal (20%)	24–48	24–72	100–500 mg	1
Second generation					
Glibenclamide	Hepatic (40%) Biliary (60%)	2–4	16–24	2.5–15 mg	1–2
Glipizide	Hepatic	2–4	6–24	2.5–40 mg	1–3
Gliclazide	Hepatic	10–12	10–24	40–320 mg	1–2
Glimepiride	Renal (60%) Biliary (40%)	5–8	12–24	1–6 mg	1
Biguanides					
Metformin	Renal	1–5	5–8	1–3 g	2–3
Meglitinides					
Repaglinide	Hepatic	1	4–6	1–16 mg	3 (with each main meal)
Nateglinide	Hepatic	1	3–4	180–540 mg	3 (with each main meal)
Thiazolidinediones					
Pioglitazone	Hepatic	5–6	16–24	15–30 mg	1
Dipeptidyl pepidase-4 inhibitors					
Sitagliptin	Renal	10–12	12–24	100 mg	1
Vildagliptin	Renal	3	10–12	50 mg	1–2
Saxagliptin	Renal and hepatic	2–3	At least 24 h	5 mg	1
Incretin mimetics					
Exenatide	Renal	2–3	Data not available	5–10 mcg	2
Liraglutide	No main organ identified	13	Data not available	0.6–1.8 mg	1

Mechanism of action of oral glucose-lowering agents.



Selecting an Oral Agent

- Often, acarbose is eliminated from consideration because slow titration is required to minimize GI effects.

- Rosiglitazone or pioglitazone also can be used as monotherapy and, like metformin, neither is likely to cause hypoglycemia, but weight gain and edema are likely. Their effects on FPG and HbA1c are intermediate between those of acarbose and metformin or the sulfonylurea.

- Both rosiglitazone and pioglitazone are associated with an approximate twofold increased risk of heart failure.

Strategy for the treatment of type 2 diabetes