Diabetes mellitus

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Introduction

- DM is a group of metabolic disorders characterized by hyperglycemia.

- It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders.

- **Microvascular** complications include neuropathy (nerve damage), nephropathy (kidney disease) and vision disorders (eg retinopathy, glaucoma, cataract and corneal disease).

- **Macrovascular** complications include heart disease, stroke and peripheral vascular disease (which can lead to ulcers, gangrene and amputation).

CLASSIFICATION OF DIABETES

- Type 1 Diabetes
- Type 2 Diabetes
- Gestational Diabetes Mellitus

Type 1 Diabetes

- This form of diabetes results from autoimmune destruction of the β cells of the pancreas.

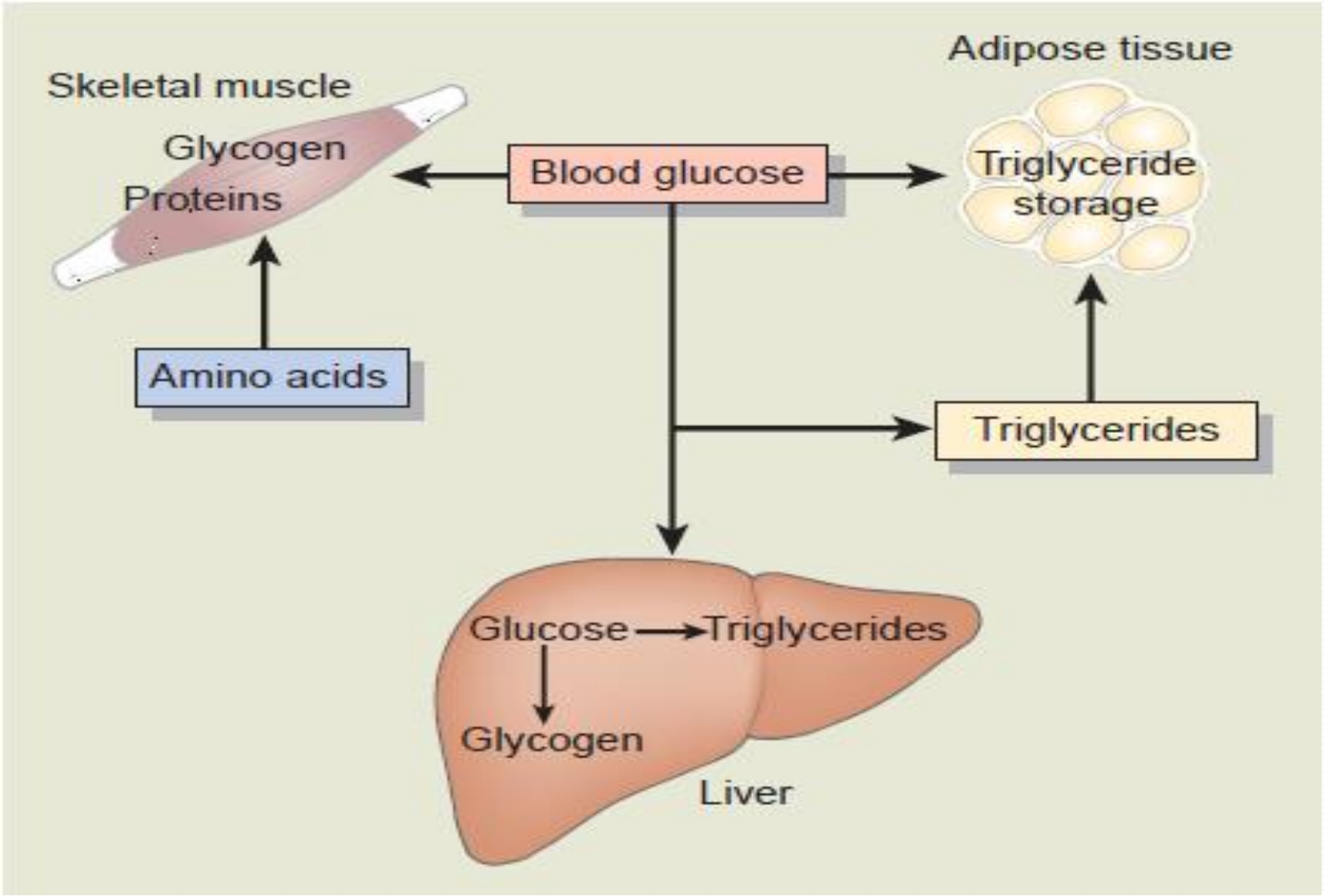
- This form of diabetes usually occurs in children and adolescents, it can occur at any age.

Type 2 Diabetes

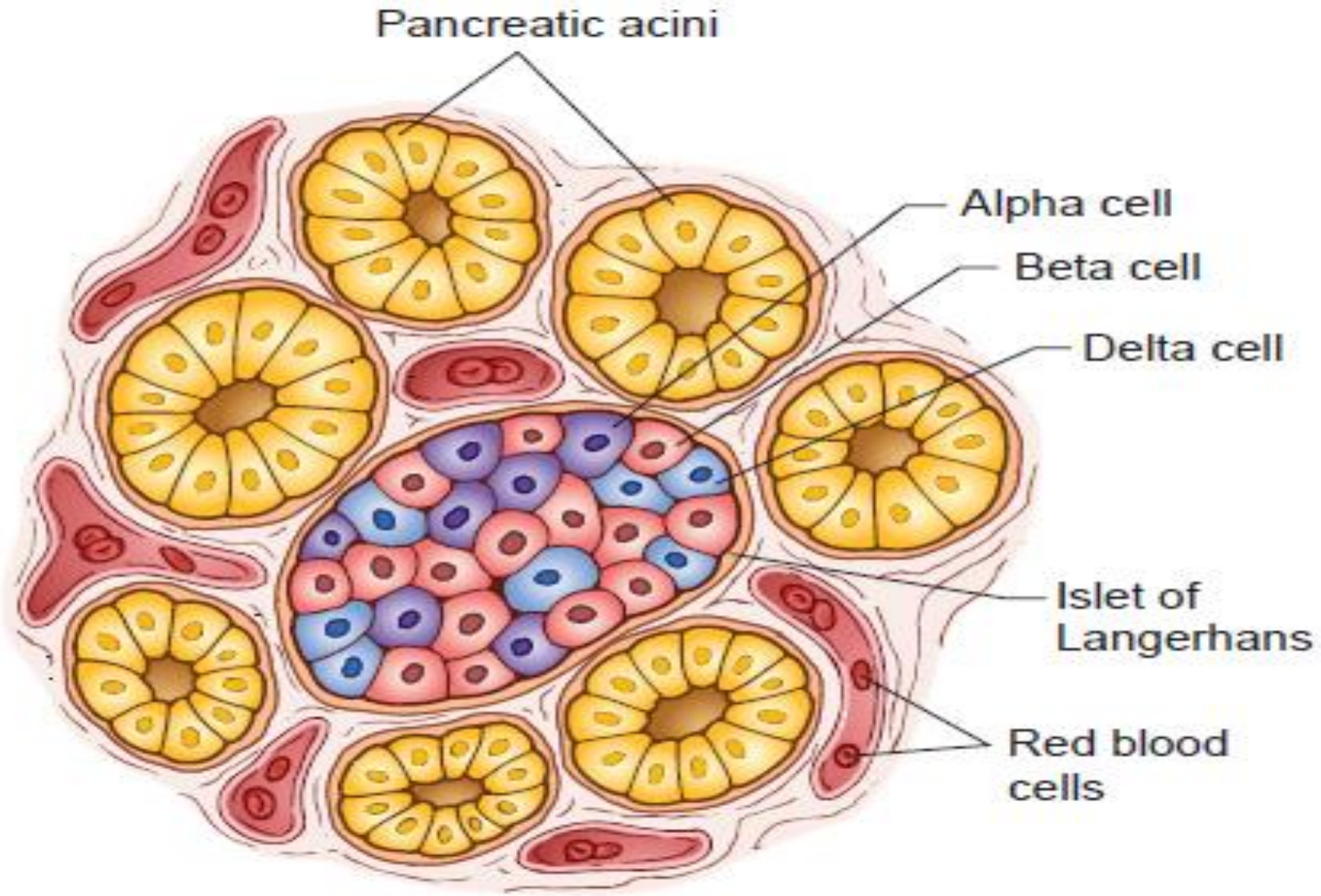
- This form of diabetes is characterized by insulin resistance impaired insulin secretion, and increased glucose production.

Gestational Diabetes Mellitus

- GDM is defined as glucose intolerance that is first recognized during pregnancy.


Adipose tissue
Skeletal muscle
Glycogen
Proteins
Blood glucose
Triglyceride storage
Amino acids
Triglycerides
Glucose
Triglycerides
Glycogen
Liver

Islets of Langerhans



	INSULIN	GLUCAGON
Glucose		
Glucose transport	Increases glucose transport into skeletal muscle and adipose tissue	
Glycogen synthesis	Increases glycogen synthesis	Promotes glycogen breakdown
Gluconeogenesis	Decreases gluconeogenesis	Increases gluconeogenesis
Fats		
Fatty acid and triglyceride synthesis	Promotes fatty acid and triglyceride synthesis by the liver	
Fat storage in adipose tissue	Increases the transport of fatty acids into adipose cells Increases conversion of fatty acids to triglycerides by increasing the availability of a-glycerol phosphate through increased transport of glucose in adipose cells	
	Maintains fat storage by inhibiting breakdown of stored triglycerides by adipose cell lipase	Activates adipose cell lipase, making increased amounts of fatty acids available to the body for use as energy
Proteins		
Amino acid transport	Increases active transport of amino acids into cells	Increases amino acid uptake by liver cells and their conversion to glucose by gluconeogenesis
Protein synthesis	Increases protein synthesis by increasing transcription of messenger RNA and accelerating protein synthesis by ribosomal RNA	
Protein breakdown	Decreases protein breakdown by enhancing the use of glucose and fatty acids as fuel	

INSULIN

- In the fasting state 75% of total body glucose disposal takes place in **non–insulin-dependent tissues**: the brain and splanchnic tissues

- The remaining 25% of glucose metabolism takes place in muscle, which is **dependent on insulin.**

- In the fed state, carbohydrate ingestion increases the plasma glucose concentration and stimulates insulin release from the pancreatic β cells.

INSULIN

- In children and adolescents, insulin is needed for normal growth and development

- Insulin is the only hormone known to have a direct effect in lowering blood glucose levels.

INSULIN

The actions of insulin are threefold:

(1) it promotes glucose uptake by target cells and provides for glucose storage as glycogen,

(2) it prevents fat , glycogen breakdown (glycogenolysis),

(3) it inhibits gluconeogenesis and increases protein synthesis

Other functions of insulin

- Insulin acts to promote fat storage by increasing the transport of glucose into fat cells.
- It also facilitates triglyceride synthesis from glucose in fat cells
- Inhibits the intracellular breakdown of stored triglycerides and reduction in the plasma free fatty acid (FFA) level..
- Inhibits protein breakdown

Pathogenesis

Type I DM

- Triggered by environmental factors, such as viruses or toxins, in genetically susceptible individuals.

- This form of diabetes is associated closely with histocompatibility antigens (**human leukocyte antigen** [HLA]-DR3 or HLA-DR4) and the presence of circulating antibodies

- The autoimmune process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens.

- The most commonly detected antibody associated with type 1 DM is the **islet cell antibody**.

- Other more readily measured circulating antibodies include **insulin autoantibodies**.

Four main steps in type 1 DM

1. A long preclinical period marked by the presence of immune markers when β-cell destruction is thought to occur;

2. Hyperglycemia when 80% to 90% of β cells are destroyed;

3. Transient remission (**Honeymoon phase**)

4. Established disease with associated risks for complications and death

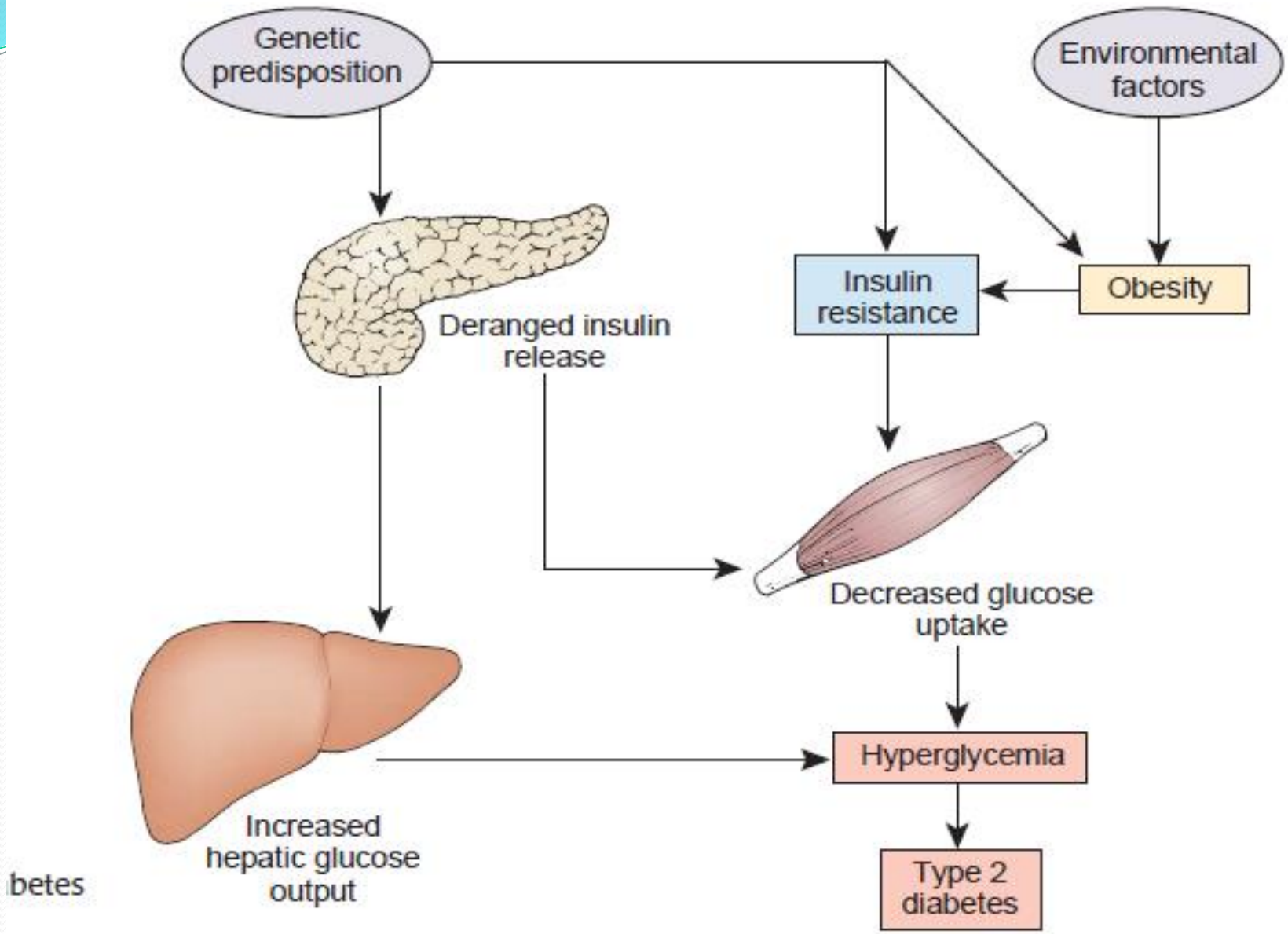
Type II DM

Type 2 diabetic individuals are characterized by

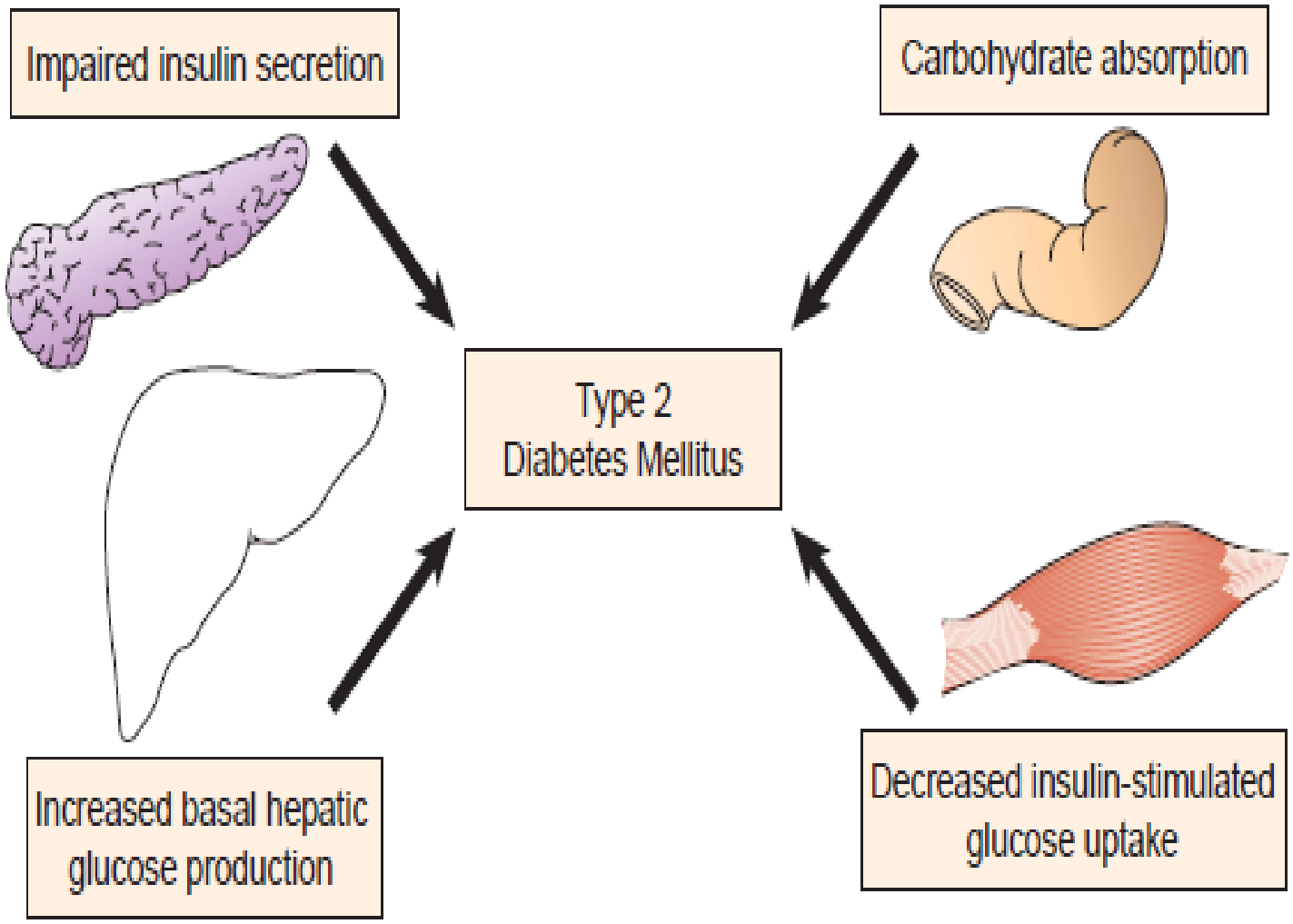
- (1) Defects in insulin secretion; and
- (2) Insulin resistance involving muscle, liver, and the adipocyte.

Impaired Insulin Secretion

- Decreased postprandial insulin secretion is caused by both **impaired pancreatic β-cell** function
- Reduced stimulus for insulin secretion from **incretin hormones**.
- The two hormones are, **glucagon-like peptide-1 (GLP-1)** and **glucose-dependent insulin-releasing peptide (GIP).**
- Incretin harmones effect is blunted


Genetic predisposition
Environmental factors
Deranged insulin release
Insulin resistance
Obesity
Decreased glucose uptake
Increased hepatic glucose output
Hyperglycemia
Type 2 diabetes

betes


Impaired insulin secretion
Carbohydrate absorption
Type 2
Diabetes Mellitus
Increased basal hepatic glucose production
Decreased insulin-stimulated glucose uptake

Insulin Resistance

Insulin resistance (IR) is a condition in which the cells of the body become resistant to the effects of insulin

or

Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect

Causes of IR

- Metabolic syndrome
- Obesity
- Pregnancy
- Infection or severe illness
- Stress
- Steroid use

Cellular Mechanisms of Insulin Resistance

Obesity and Insulin Resistance

- Weight gain leads to insulin resistance.
- The increase in insulin resistance with weight gain is directly related to the amount of **visceral adipose tissue** (fat cells located within the abdominal cavity)
- This fat tissue has been shown to have a **higher rate of lipolysis** than subcutaneous fat, resulting in an **increase in FFA** production.

These fatty acids stimulate the production of

- **Very low-density lipoproteins** and
- **Decrease insulin sensitivity** in peripheral tissues.

- VAT also produces a number of **cytokines** that cause insulin resistance.

- Elevated plasma FFA levels, as well as increased triglyceride/fatty acyl coenzyme A (CoA) content in muscle, liver, and β cells, lead to the development of muscle/hepatic **insulin resistance and impaired insulin secretion**.

- **Adiponectin** is secreted by adipose tissue and circulates in the blood.

- It has been shown that decreased levels of adiponectin coincide with insulin resistance in patients with obesity and type 2 diabetes.

The Metabolic Syndrome

- The association of insulin resistance with a clustering of cardiovascular risk factors including hyperinsulinemia, hypertension, abdominal obesity, dyslipidemia, and coagulation abnormalities has been referred to by a variety of names including "**the insulin resistance syndrome**," "**the metabolic syndrome**," "**the dysmetabolic syndrome**," and **Syndrome X**

Sites of Insulin Resistance

Liver

- Following glucose ingestion, insulin is secreted which suppresses glucagon secretion and reduces hepatic glucose output

- Type 2 diabetic patients fail to suppress glucagon in response to a meal and can even have a paradoxical rise in glucagon levels.

- Thus, hepatic insulin resistance and hyperglucagonemia result in **continued production of glucose by the liver**

Peripheral (Muscle)

- Muscle is the major site of glucose disposal
- Insulin resistance decrease muscle glucose uptake
- The primary site of insulin resistance in type 2 diabetic subjects resides in muscle

Peripheral (Adipocyte)

- Insulin is a **potent inhibitor** of lipolysis, and holds the release of FFAs from the adipocyte by inhibiting the **hormone-sensitive lipase enzyme.**

Risk factors for type II DM

- Family history of diabetes
- Physical inactivity
- History of PCOS,
- Clinical conditions associated with insulin resistance (e.g., severe obesity
- Hypertension (≥140/90 mmHg or on antihypertensive therapy)
- Dyslipidemia
- HDL-C <35 mg/dL (0.90 mmol/L)
- Triglyceride >250 mg/dL (2.82 mmol/L)
- Cardiovascular disease

Symptoms

Type I

Polyuria, polydipsia, polyphagia, and weight loss, diabetic ketoacidosis, Hyperglycemic Hyperosmolar State.

Type II

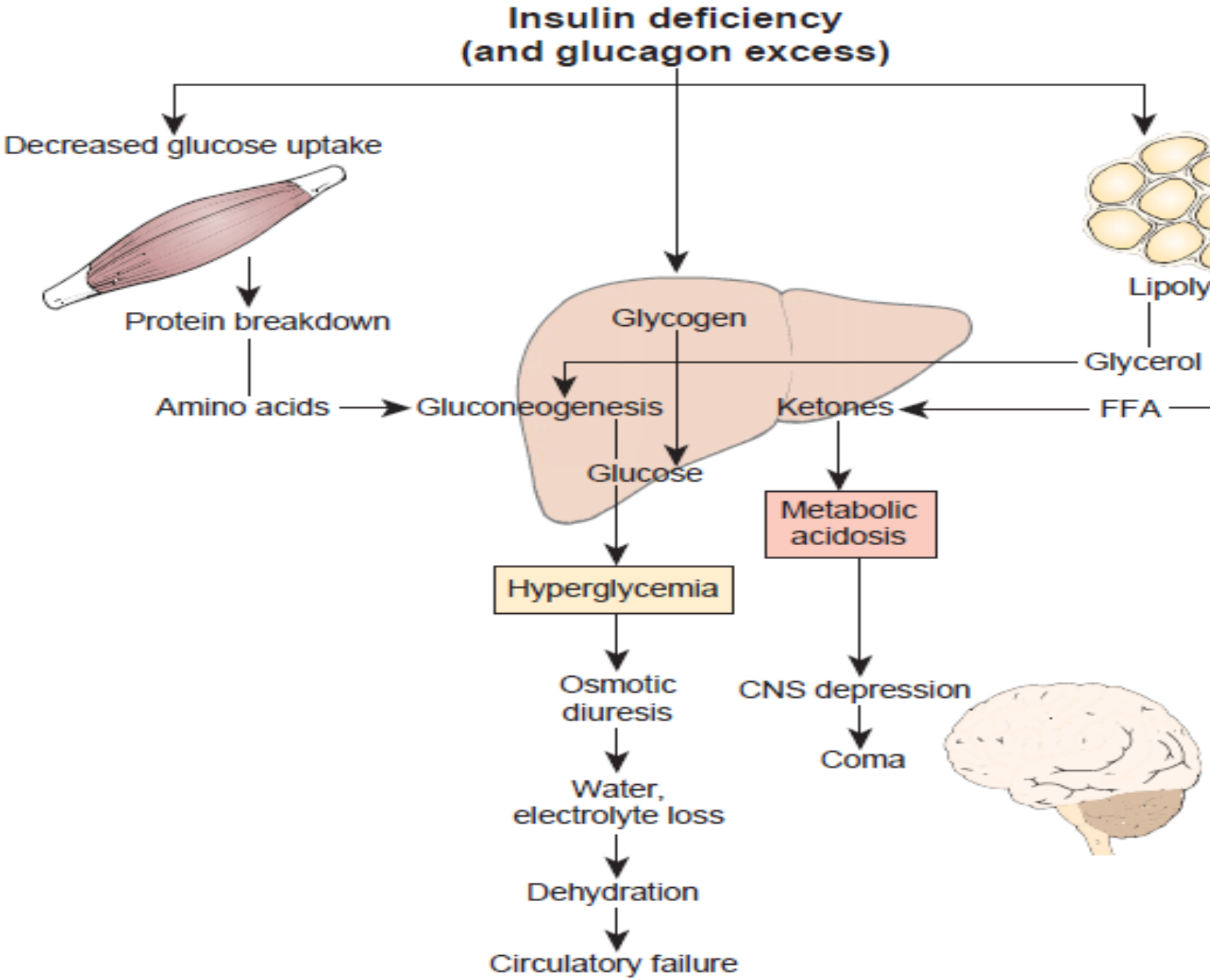
Lethargy, Polyuria, Nocturia, and Polydipsia

Acute Complications of DM

- Diabetic Ketoacidosis
- Hyperglycemic Hyperosmolar State

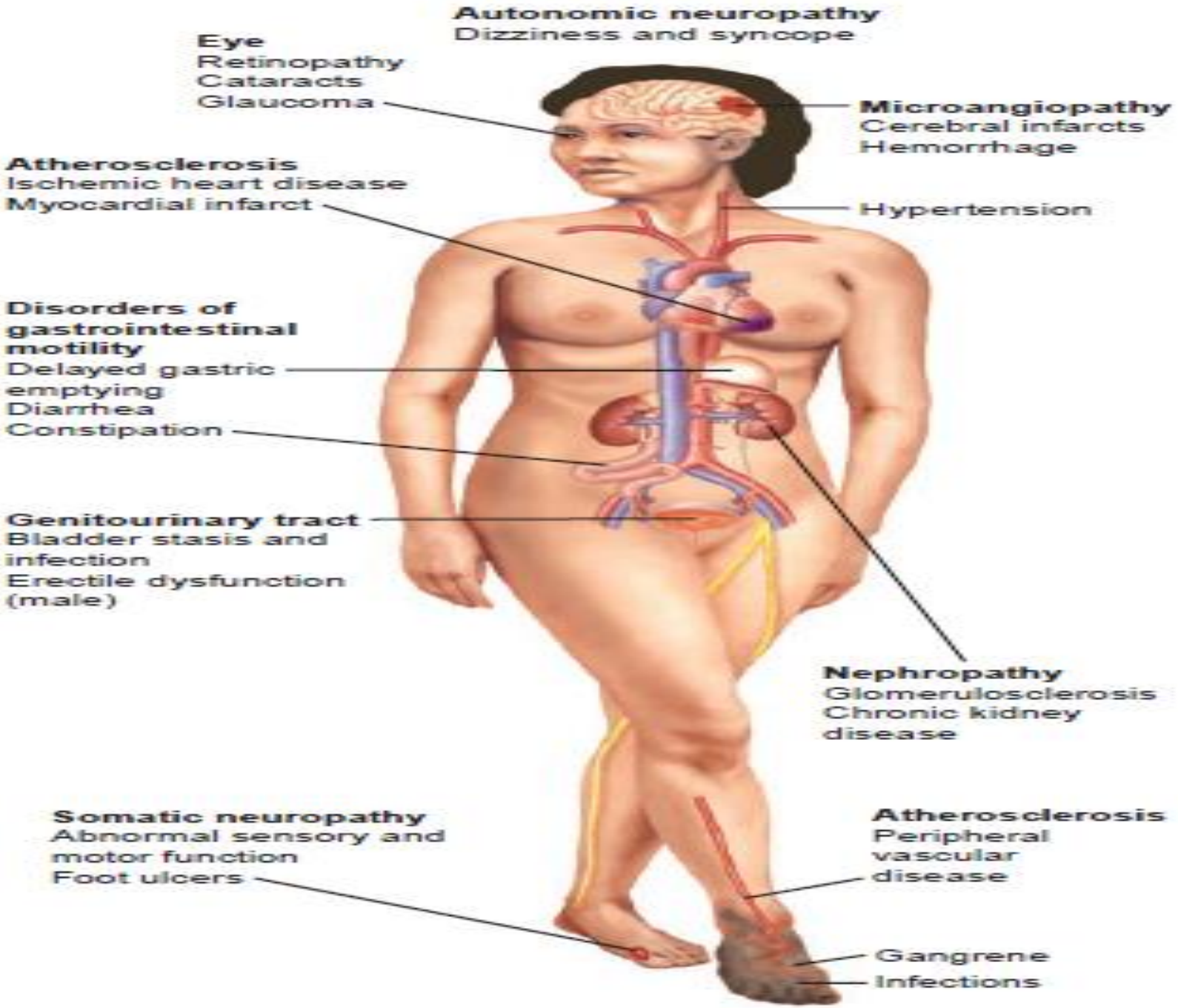
Chronic Complications of DM

- Microvascular
- Macrovascular
- Others
    - Gastrointestinal (gastroparesis, diarrhea)
    - Genitourinary (uropathy/sexual dysfunction)
    - Dermatologic
    - Infectious
    - Cataracts
    - Glaucoma


Insulin deficiency
(and glucagon excess)
Decreased glucose uptake
Protein breakdown
Amino acids
Gluconeogenesis
Glycogen
Glucose
Hyperglycemia
Osmotic diuresis
Water, electrolyte loss
Dehydration
Circulatory failure
Lipolysis
Glycerol
FFA
Ketones
Metabolic acidosis
CNS depression
Coma

Plasma glucose values

TEST	NORMOGLYCEMIC	IFG†	IGT†	DM‡
FPG	<100 mg/dL (5.6 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L)		≥126 mg/dL (7.0 mmol/L)
2-hour OGTT§	<140 mg/dL (7.8 mmol/L)		140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Other				Symptoms of DM and casual plasma glucose ≥200 mg/dL (11.1 mmol/L)


Autonomic neuropathy
Dizziness and syncope
Eye
Retinopathy
Cataracts
Glaucoma
Microangiopathy
Cerebral infarcts
Hemorrhage
Atherosclerosis
Ischemic heart disease
Myocardial infarct
Hypertension
Disorders of gastrointestinal motility
Delayed gastric emptying
Diarrhea
Constipation
Genitourinary tract
Bladder stasis and infection
Erectile dysfunction (male)
Nephropathy
Glomerulosclerosis
Chronic kidney disease
Somatic neuropathy
Abnormal sensory and motor function
Foot ulcers
Atherosclerosis
Peripheral vascular disease
Gangrene
Infections

Diagnosis

Fasting plasma glucose (FPG)

Normal

- FPG <100 mg/dL (5.6 mmol/L)

Impaired fasting glucose (IFG)

- 100–125 mg/dL (5.6–6.9 mmol/L)

Diabetes mellitus

- FPG =126 mg/dL (7.0 mmol/L)

2-Hour postload plasma glucose (oral glucose tolerance test)

Normal

- Postload glucose <140 mg/dL (7.8 mmol/L)

Impaired glucose tolerance (IGT)

- 2-hour postload glucose 140–199 mg/dL (7.8–11.1 mmol/L)

Diabetes mellitus

- 2-hour postload glucose =200 mg/dL (11.1 mmol/L)

According to ADA, diagnosis of diabetes can be made when one of the following is present

- Classic signs and symptoms of diabetes (polyuria, polydipsia, ketonuria, and unexplained weight loss) combined with a random plasma glucose ≥200 mg/dL.
- FPG ≥126 mg/dL.
- After a standard oral glucose challenge (75 g glucose for an adult or 1.75 g/kg for a child)
    - Venous plasma glucose concentration is ≥200 mg/dL at 2 hours and >200 mg/dl or at least one other time during the test (0.5, 1, 1.5 hours).

Thank you