Diabetes Mellitus

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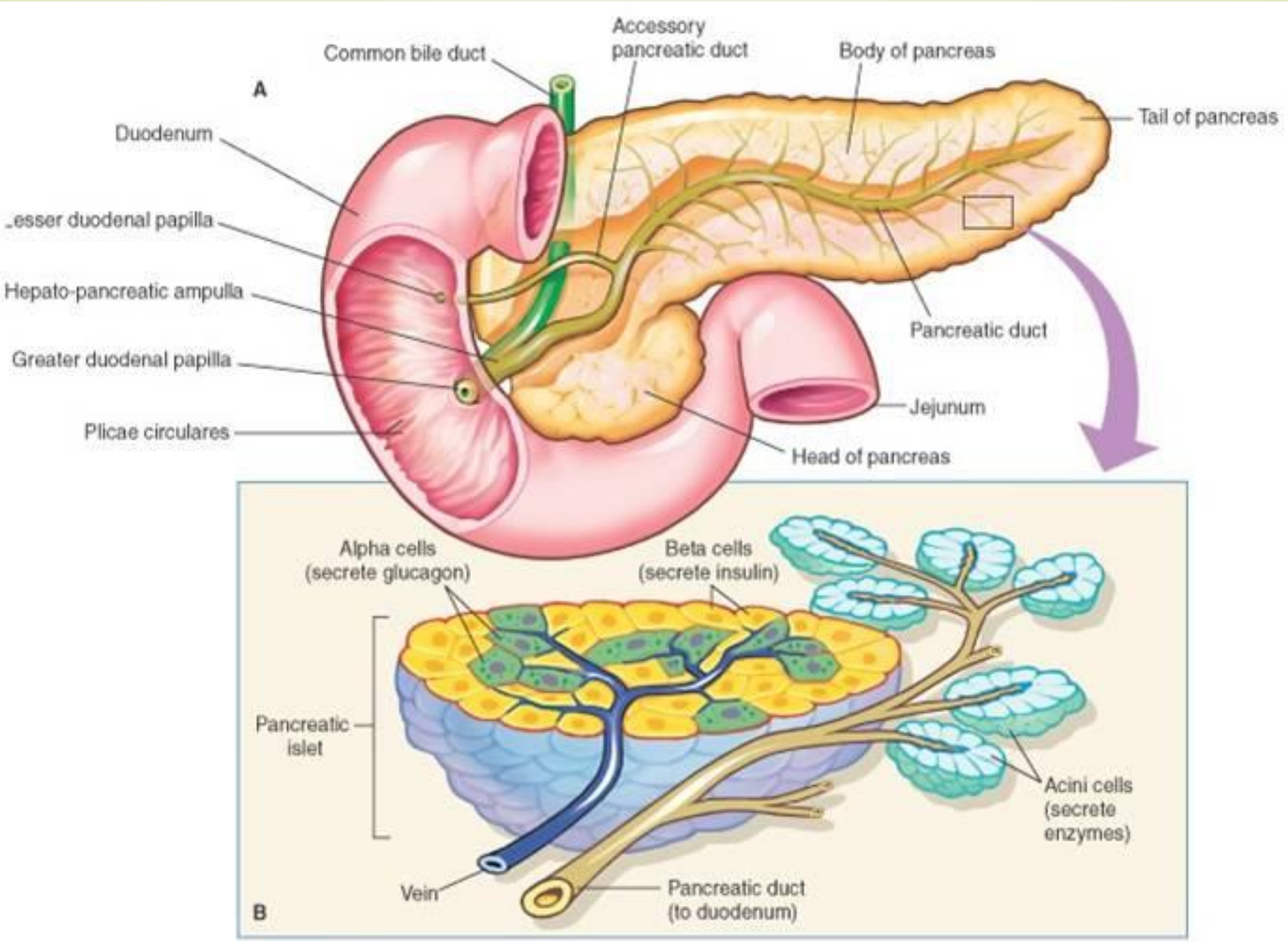
Objectives

- Understand the structure of the pancreas and have a basic understanding of its function.
- The student should have an understanding of the pathogenesis and major histopathological changes seen in diabetes mellitus type 1 and type 2.
- The student should recognize the major complications of diabetes mellitus.


A
Common bile duct
Accessory pancreatic duct
Body of pancreas
Tail of pancreas
Duodenum
Lesser duodenal papilla
Hepato-pancreatic ampulla
Greater duodenal papilla
Plicae circulares
Pancreatic duct
Jejunum
Head of pancreas
Alpha cells (secrete glucagon)
Beta cells (secrete insulin)
Pancreatic islet
Acini cells (secrete enzymes)
Vein
Pancreatic duct (to duodenum)
B

THE ENDOCRINE PANCREAS

- ***islets of Langerhans*, contain four major cell types :β, α, δ, and PP (pancreatic polypeptide) cells.**
- *The β cell produces insulin*
- *The α cell secretes glucagon .*
- δ cells contain somatostatin
- *PP cells contain a unique pancreatic polypeptide.* that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes

Diabetes Mellitus (DM)

*Diabetes mellitus is not a single disease entity but rather a *group of metabolic disorders sharing the common underlying feature of* ***hyperglycemia*****.**

***Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both.**

***Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations in USA.**

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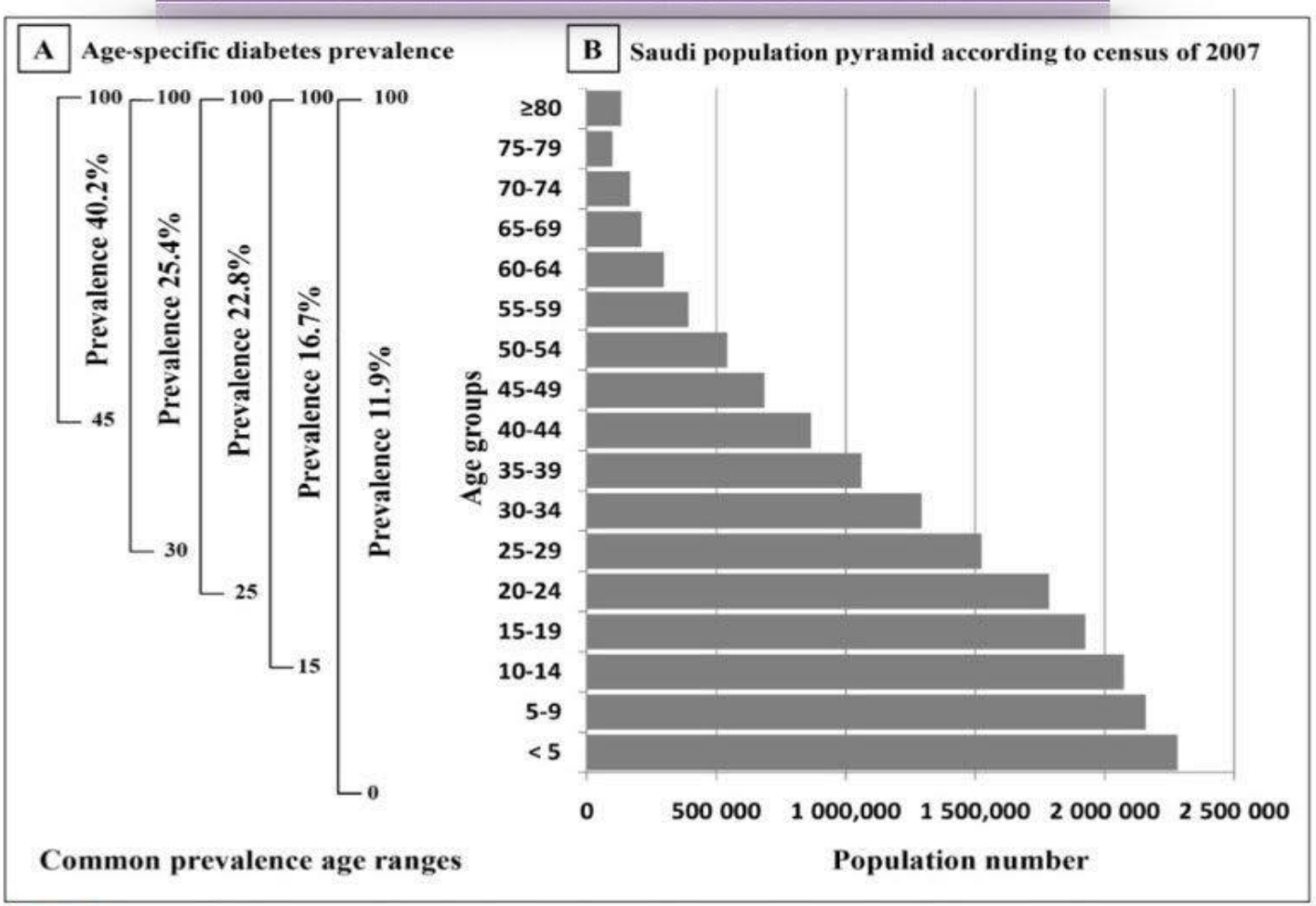

Figure 1 Age-specific diabetes prevalence in relation to the population pyramid according to the census 2007

Al-Rubeaan K. et al. Ann Saudi Med,2014

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Diabetes Mellitus (DM)

Prediabetes, **defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes .**

persons with prediabetes have an elevated risk for development of frank diabetes

Diagnosis of DM

Blood glucose is normally maintained in a very narrow range, usually 70 to 120 mg/dL.

According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diagnostic criteria for diabetes include the following:

A fasting plasma glucose greater than or equal to 126 mg/dL, and/or

2. A random plasma glucose greater than or equal to 200 mg/dL (in a patient with classic hyperglycemic signs, discussed later), and/or

3. A 2-hour plasma glucose greater than or equal to 200 mg/dL during an oral glucose tolerance test with a loading dose of 75 gm, and/or

4. A glycated hemoglobin (HbA1C) level greater than or equal to 6.5% (glycated hemoglobin is further discussed under chronic complications of diabetes)

- All tests, except the random blood glucose test in a patient with classic hyperglycemic signs, need to be repeated and confirmed on a separate day.
- Of note, many acute conditions associated with stress, such as severe infections, burns, or trauma, can lead to transient hyperglycemia due to secretion of hormones such as catecholamines and cortisol that oppose the effects of insulin.

- The diagnosis of diabetes requires persistence of hyperglycemia following resolution of the acute illness

Prediabetes

- **Impaired glucose tolerance (prediabetes) is defined as:**
- 1. A fasting plasma glucose between 100 and 125 mg/dL ("impaired fasting glucose"), and/or
- 2. A 2-hour plasma glucose between 140 and 199 mg/dL during an oral glucose tolerance test, and/or
- 3. HbA1C level between 5.7% and 6.4%
- As many as one-fourth of individuals with impaired glucose tolerance will develop overt diabetes in the next 5 years, with additional risk factors such as obesity and family history compounding such risk.
- In addition, individuals with prediabetes have an elevated risk of cardiovascular disease.

Table 20.5 Simplified Classification of Diabetes

1. *Type 1 Diabetes*
   Beta cell destruction, usually leading to absolute insulin deficiency
2. *Type 2 Diabetes*
   Combination of insulin resistance and beta cell dysfunction
3. *Genetic Defects of Beta Cell Function*
   Maturity-onset diabetes of the young (MODY) (see text)
   Insulin gene mutations
4. *Genetic Defects in Insulin Action*
   Insulin receptor mutations
5. *Exocrine Pancreatic Defects*
   Chronic pancreatitis
   Pancreatectomy
   Cystic fibrosis
   Hemochromatosis
6. *Endocrinopathies*
   Growth hormone excess (acromegaly)
   Cushing syndrome
   Hyperthyroidism
   Pheochromocytoma
7. *Infections*
   Cytomegalovirus infection
   Coxsackievirus B infection
   Congenital rubella
8. *Drugs*
   Glucocorticoids
   Thyroid hormone
   β-Adrenergic agonists
9. *Gestational Diabetes*
   Diabetes associated with pregnancy

Modified from Diagnosis and classification of diabetes mellitus (American Diabetes Association). *Diabetes Care* 37:S81-S90; 2014.

- • **Type 1 diabetes** is an autoimmune disease characterized by pancreatic β-cell destruction and an absolute deficiency of insulin.

It accounts for approximately 5% to 10% of all cases, and is the most common subtype diagnosed in patients younger than 20 years of age.

- • **Type 2 diabetes** is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells ("relative insulin deficiency"). Approximately 90% to 95% of diabetic patients have type 2 diabetes, and many of them are overweight.

Although classically considered "adult-onset," the prevalence of type 2 diabetes in children and adolescents is increasing at an alarming pace due to the increasing rates of obesity in these age groups.

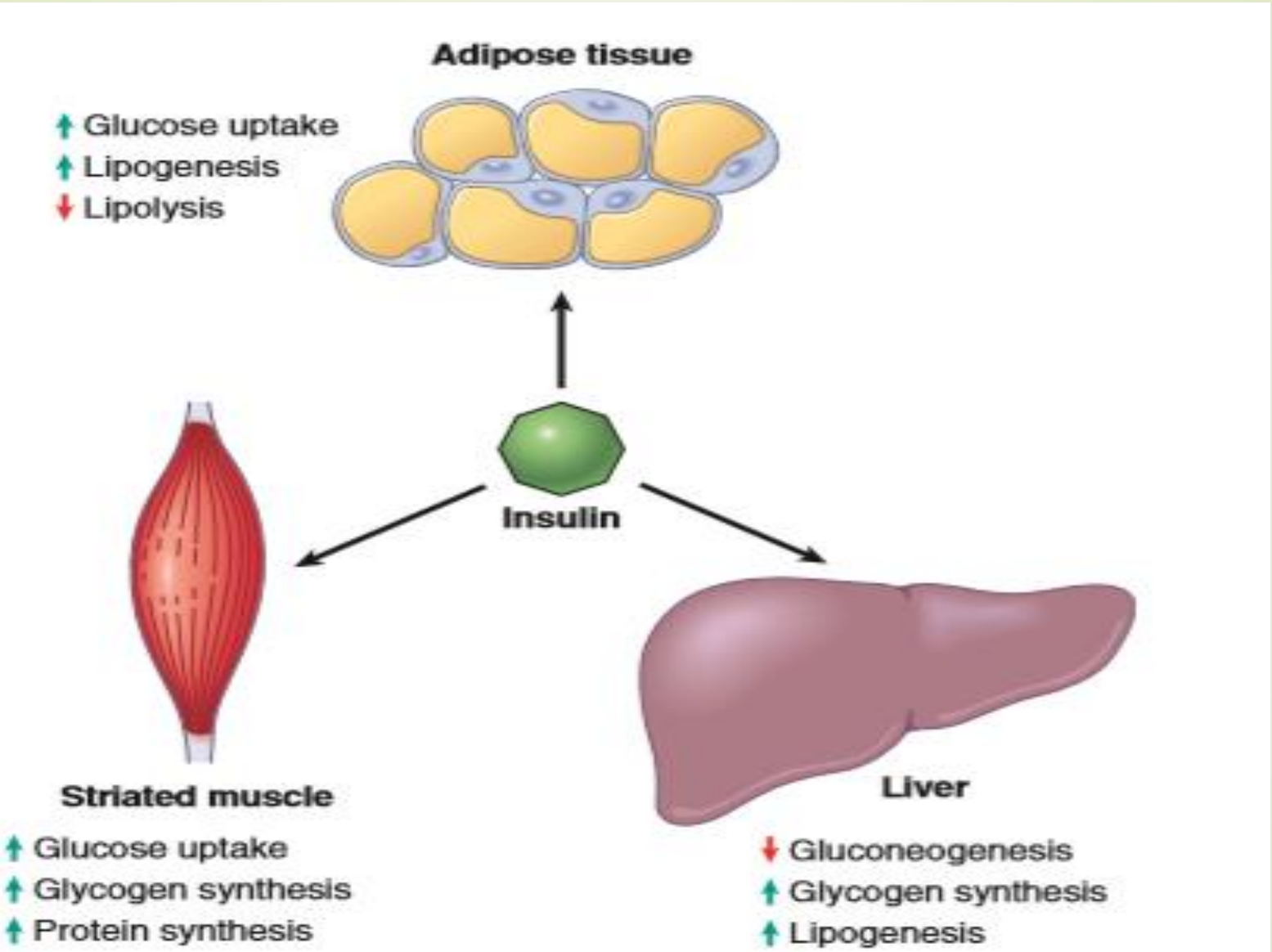


Fig. 20.21 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

Pathogenesis

- **Type 1 diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens.**
- The classic manifestations of the disease occur late in its course, after more than 90% of the beta cells have been destroyed. **The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells specific for Beta cell antigens.**
- **autoantibodies** against a variety of beta cell antigens, are detected in the blood of 70% to 80% of patients.
- **genetic susceptibility** :90% and 95% of white patients with type 1 diabetes have ***HLA-DR3, or DR4. Several non-HLA genes also increase susceptibility to type 1 diabetes***
- **environmental factors,** especially infections, may be involved in type 1 diabetes.

PATHOGENESIS

Type 2 diabetes is a heterogeneous and multifactorial complex disease that involves interactions of genetics, environmental risk factors, and inflammation.

Unlike type 1 diabetes, however, there is no evidence of an autoimmune basis.

The two defects that characterize type 2 diabetes are:

(1) a decreased ability of peripheral tissues to respond to insulin (insulin resistance) and

(2) beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia

1- Insulin resistance

- **Insulin resistance** is defined as the failure of target tissues to respond normally to insulin. The liver, skeletal muscle, and adipose tissue are the major tissues

Obesity and Insulin Resistance

- metabolic syndrome has been applied to a constellation of findings dominated by visceral obesity, accompanied by insulin resistance, glucose intolerance, and cardiovascular risk factors such as hypertension and abnormal lipid profiles.
- Individuals with metabolic syndrome are at high risk for the development of type 2 diabetes.

- central obesity (abdominal fat) is more likely to be associated with insulin resistance than is peripheral (gluteal/ subcutaneous) obesity

Obesity can adversely impact insulin sensitivity in numerous ways

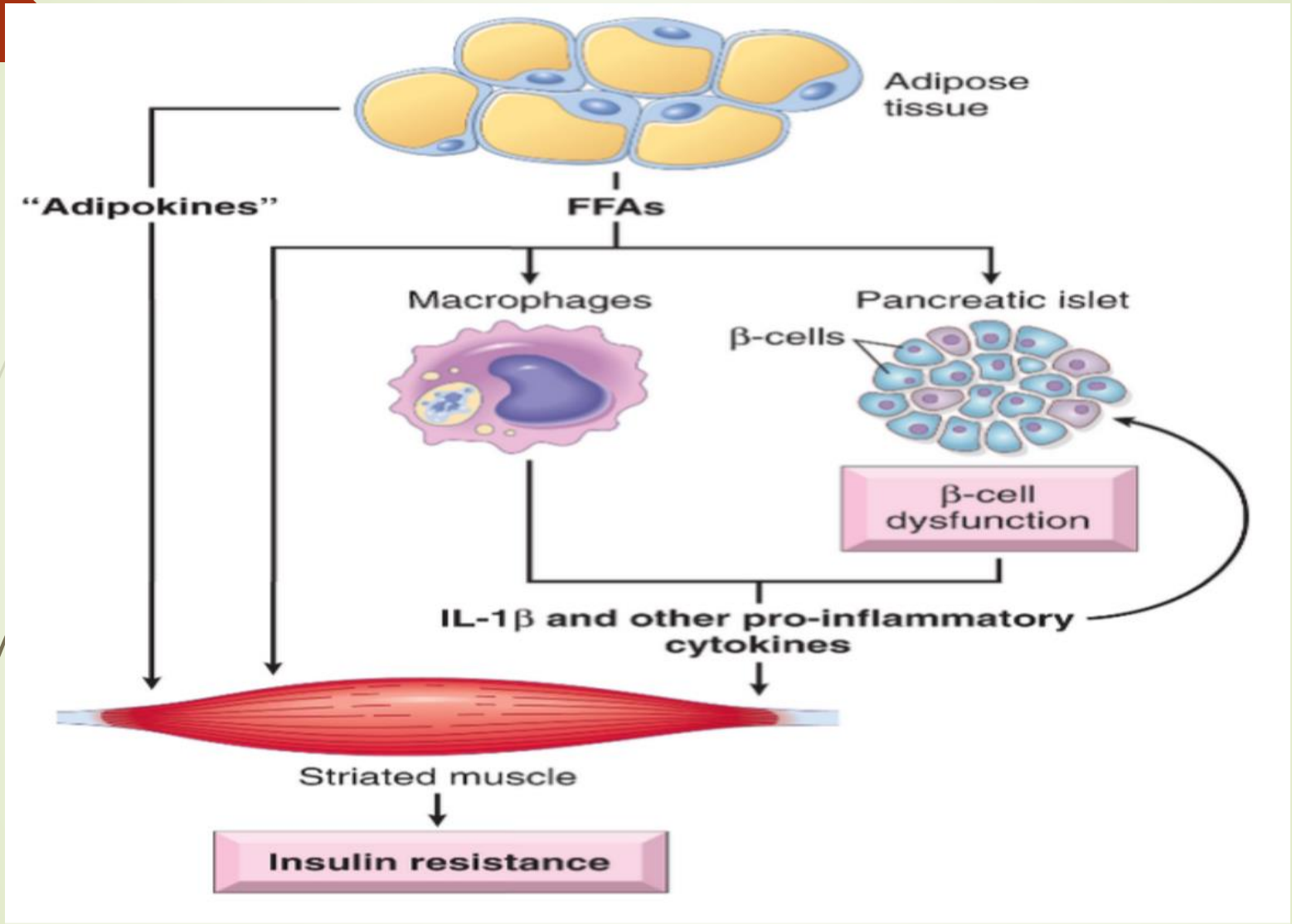
- Excess FFAs: studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity

- Adipokines: Some of these promote hyperglycemia, and others (such as leptin and adiponectin) decrease blood glucose, by increasing the insulin sensitivity in the peripheral tissues. Adiponectin levels are decreased in obesity, thus contributing to insulin resistance.
- Inflammation: Excess FFAs within macrophages and beta cells can activate the inflammasome, a multiprotein cytoplasmic complex that leads to secretion of the cytokine interleukin , as well as other cytokines promote insulin resistance in peripheral tissues.

2- Beta cell dysfunction.

- Beta Cell Dysfunction :

While insulin resistance by itself can lead to impaired glucose tolerance, beta cell dysfunction is an essential component in the development of overt diabetes


Adipose tissue
"Adipokines"
FFAs
Macrophages
Pancreatic islet
β-cells
β-cell dysfunction
IL-1β and other pro-inflammatory cytokines
Striated muscle
Insulin resistance

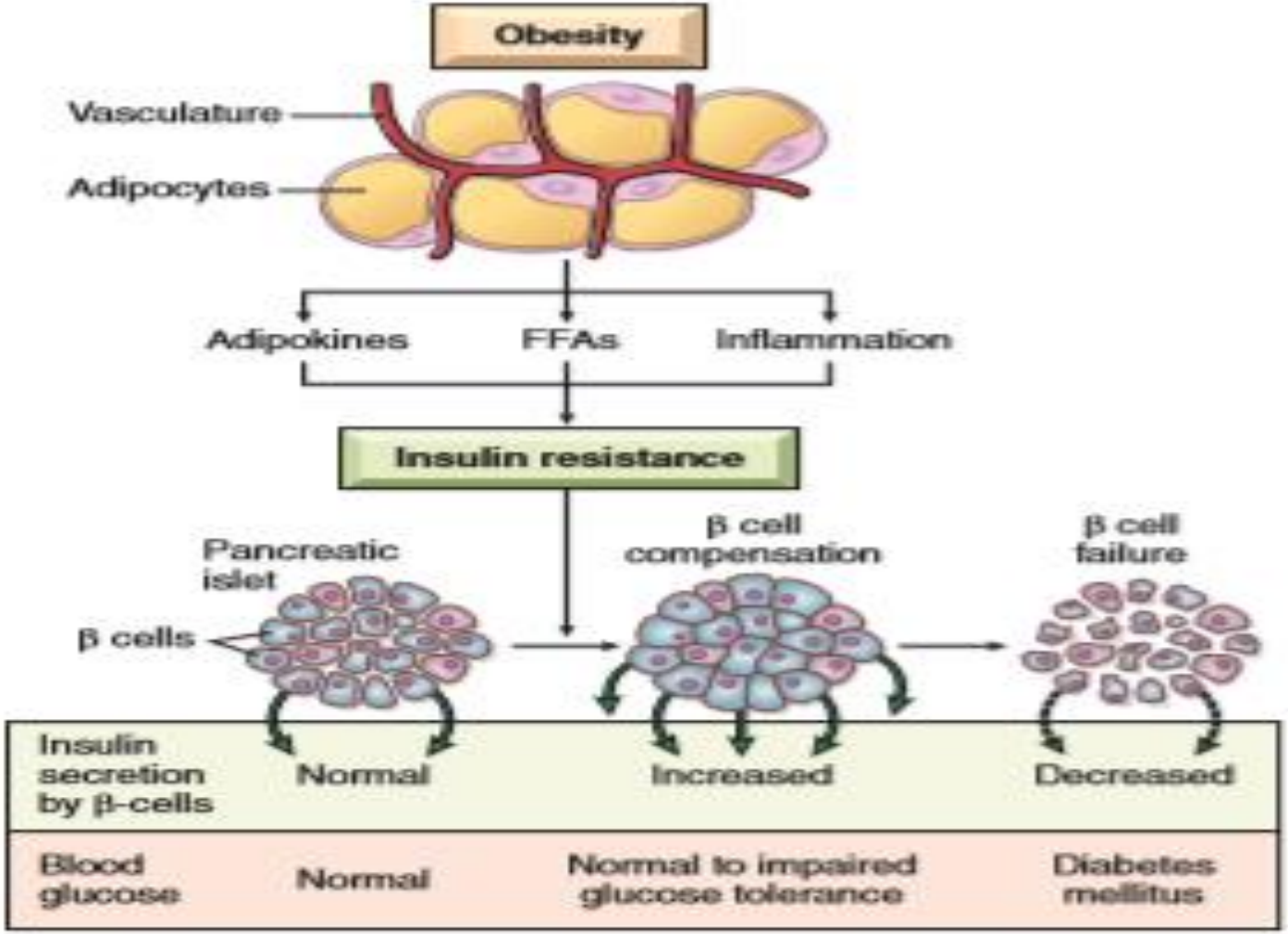


Fig. 20.23 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β cell compensation is followed by β cell failure, and diabetes ensues. *(Reproduced with permission from Kasuga M: Insulin resistance and pancreatic β-cell failure. J Clin Invest 116:1756, 2006.)*

Monogenic Forms of Diabetes

- Type 1 and type 2 diabetes are genetically complex ,no single-gene defect (mutation) can account for predisposition to these entities.
- By contrast, monogenic forms of diabetes are uncommon examples of the *diabetic phenotype occurring as a result of loss-of-function mutations within a single gene*.
- Monogenic causes of diabetes include primary defects in beta cell function and insulin receptor signaling.
- Monogenic diabetes can be classified based on age of onset into: *congenital early onset diabetes (manifesting in the neonatal period) and *maturity onset diabetes of the young (MODY), which develops beyond the neonatal period but usually before 25 years of age.

Gestational diabetes.

- Pregnancy is a "diabetogenic" state in which the prevailing hormones favors a state of insulin resistance. In some euglycemic pregnant women this can give rise to gestational diabetes.
- Women with pregestational diabetes (where hyperglycemia is already present in the periconception period) have an increased risk for stillbirth and congenital malformations in the fetus
- fetal overgrowth (macrosomia) occurs because maternal hyperglycemia can induce compensatory secretion of insulin-like growth factors in the fetus.

Acute Metabolic Complications of Diabetes

- Type 1 : Although beta cell destruction is a gradual process, the transition from impaired glucose tolerance to overt diabetes may be abrupt.
- The onset of diabetes is marked by polyuria, polydipsia, polyphagia (known as the classic triad of diabetes), and in severe cases, ketoacidosis, all resulting from metabolic derangements
- The combination of polyphagia and weight loss is paradoxical and should always point to the possibility of diabetes.

Diabetic Ketoacidosis (Type 1)

- In type 1 diabetes: any forms of stress may worsen the metabolic imbalance, leading to diabetic ketoacidosis. The plasma glucose usually is in the range of 500 to 700 mg/dL
- The marked hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state.
- The second major effect is activation of the ketogenic machinery. Insulin deficiency leads to excessive breakdown of adipose stores, giving rise to increased FFAs, which are oxidized by the liver to produce ketones as a source of energy for consumption by vital organs (e.g., the brain). The rate at which ketones are formed may exceed the rate at which they can be used by peripheral tissues, leading to ketonemia and ketonuria.
- the accumulating ketones decrease blood pH, resulting in metabolic acidosis.

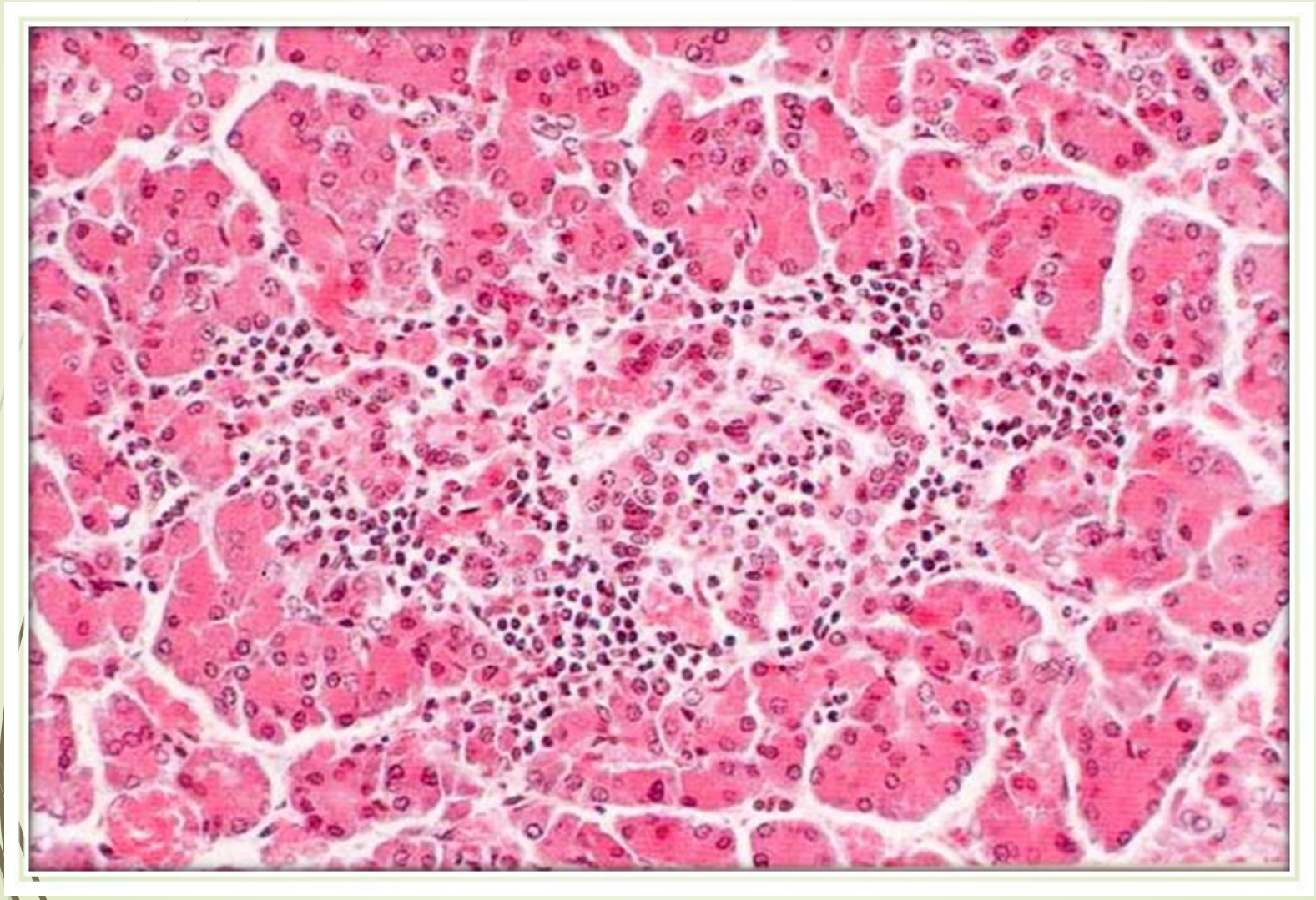
Hyperosmolar Non-ketotic Coma (Type 2)

- patients with type 2 diabetes may develop hyperosmolar nonketotic coma.
- severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia.
- Typically, the affected individual is an older adult diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.

Morphology

- Lesions in the pancreas are inconstant and rarely of diagnostic value. One or more of the following alterations may be present:
- **Reduction in the number and size of islets.** This change most often is seen in type 1 diabetes.
- **Leukocytic infiltration of the islets,** (insulitis) are principally composed of T lymphocytes. They are most often seen type 1 diabetes at the time of clinical presentation
- **Amyloid replacement of islets in long-standing type 2 diabetes,** appearing as deposition of pink, amorphous material. At advanced stages fibrosis also may be observed
- An increase in the number and size of islets, especially characteristic of nondiabetic newborns of diabetic mothers.

Insulitis



Amyloidosis

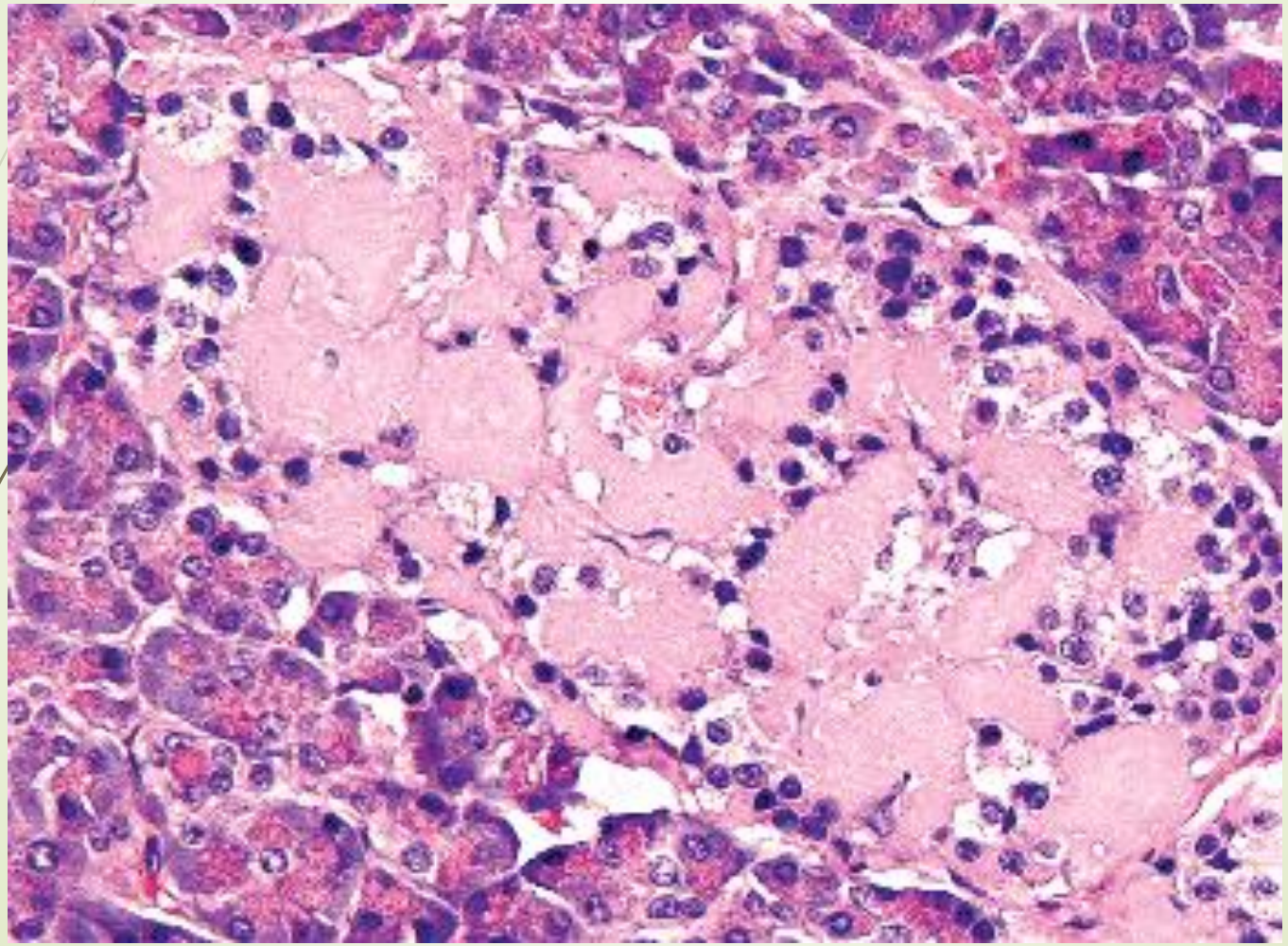


Table 20.6 Type I Versus Type 2 Diabetes Mellitus

Type I Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset usually in childhood and adolescence	Onset usually in adulthood; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority of patients are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma
Genetics	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes
Pathogenesis	
Breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by beta cells Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Autoimmune "insulitis"	Amyloid deposition in islets (late)
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, Human leukocyte antigen; *MHC*, major histocompatibility complex.

Chronic Complications of Diabetes

- The morbidity associated with long-standing diabetes of any type results from the chronic complications of hyperglycemia, and the resulting damage induced in both

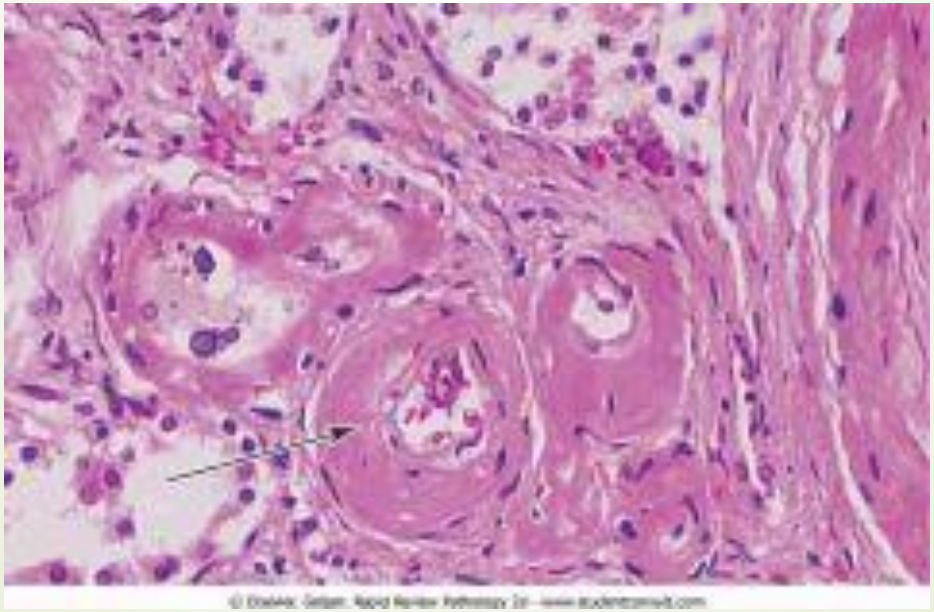
**large- and medium-sized muscular arteries (diabetic macrovascular disease)

**small-vessels (diabetic microvascular disease).

Diabetic complications: Macrovascular Disease.

- The hallmark of diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large and medium-sized arteries.
- Myocardial infarction, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics
- Gangrene of the lower extremities, as a result of advanced vascular disease
- The larger renal arteries also are subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation.

- **Hyaline arteriolosclerosis,** the vascular lesion associated with hypertension , is both more prevalent and more severe in diabetics than in nondiabetics
- It takes the form of an amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen



Diabetic complication: Microangiopathy.

- One of the most consistent morphologic features of diabetes is **diffuse thickening of basement membranes.** The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla
- the basal lamina separating parenchymal or endothelial cells from the surrounding tissue is markedly thickened by concentric layers of hyaline material composed predominantly of type IV collagen . Of note, **despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.**
- **The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.**

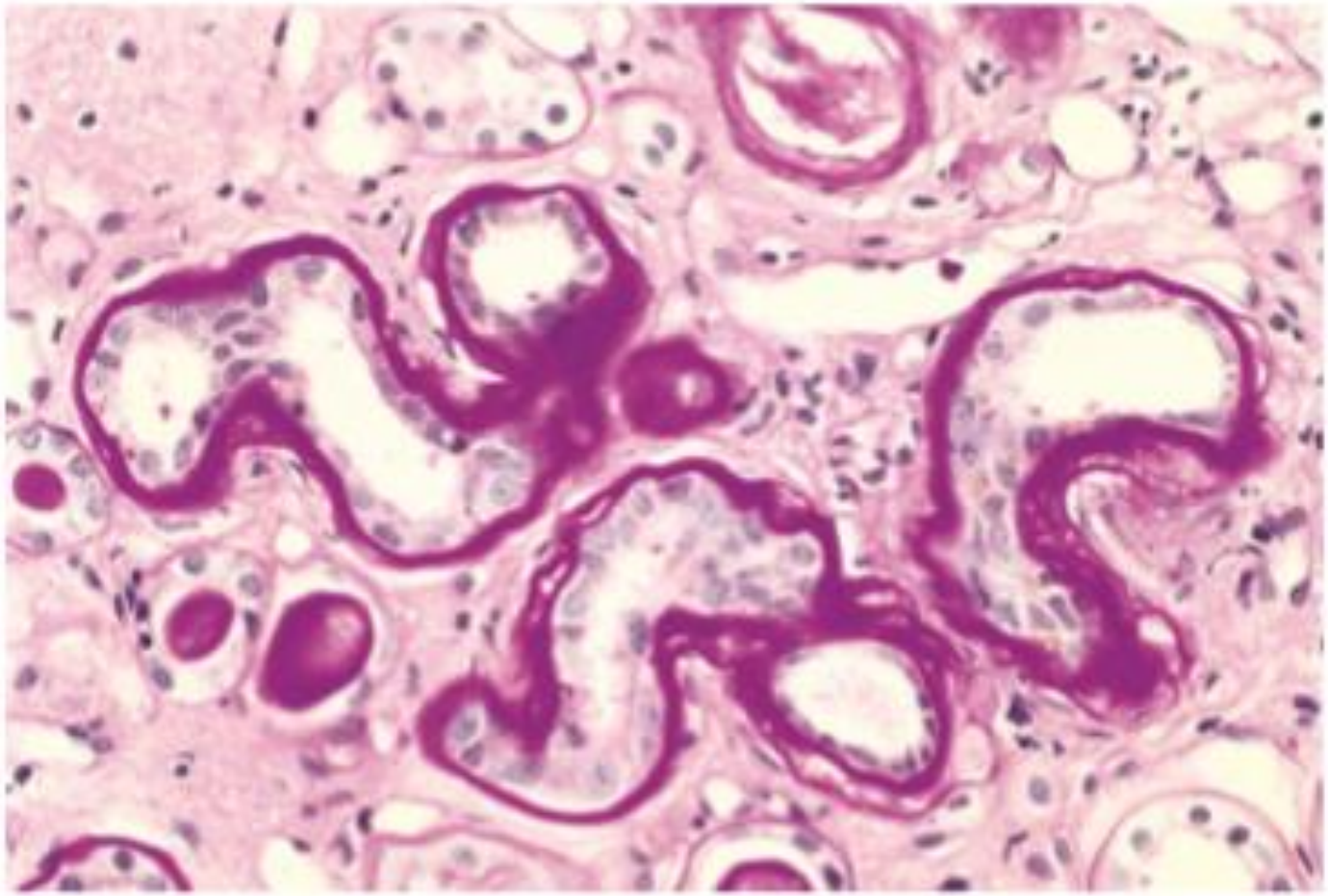


Fig. 20.28 Renal cortex showing thickening of tubular basement membranes in a specimen from a diabetic patient. (Periodic acid–Schiff stain.)

Diabetic complication: Nephropathy

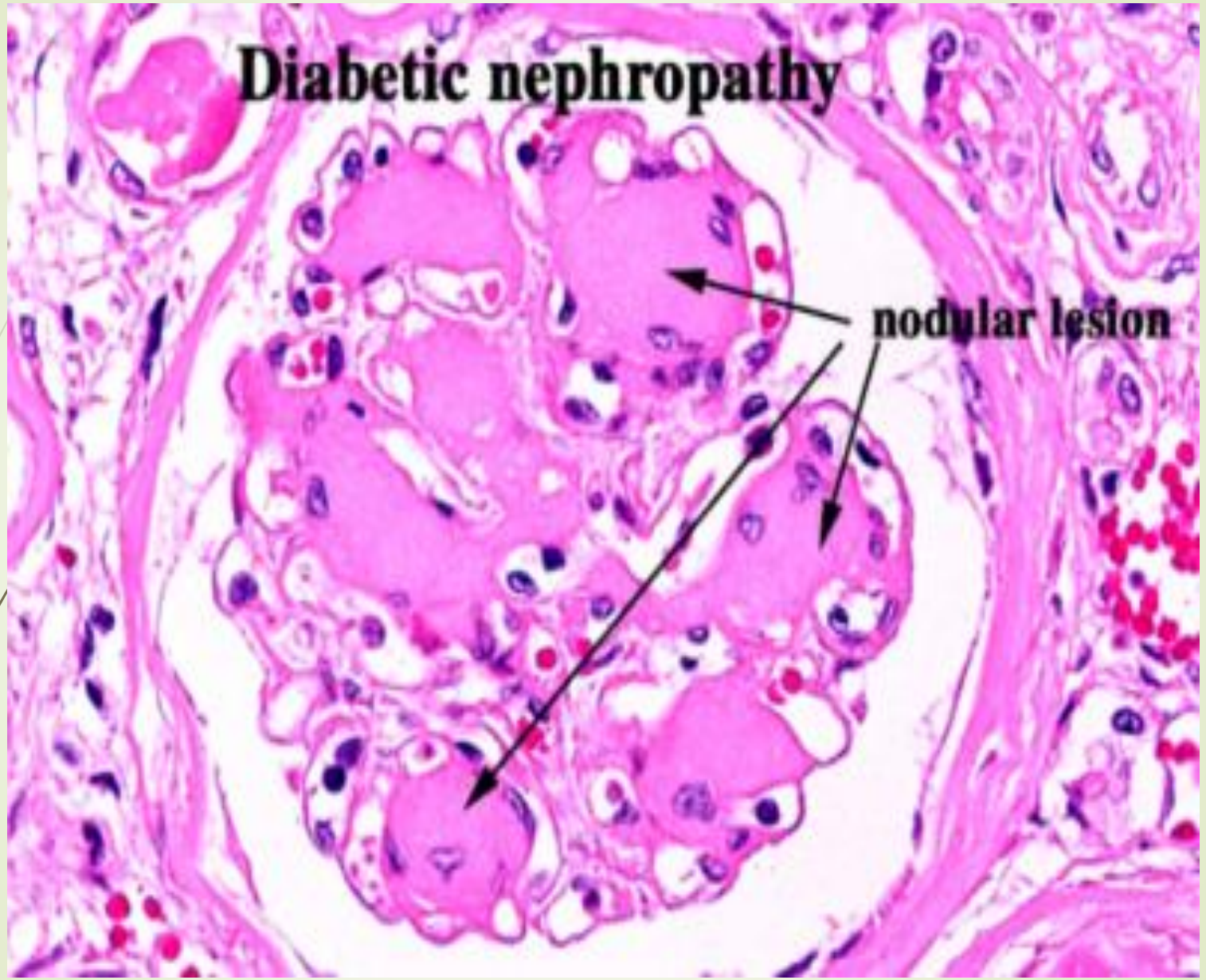
- Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered:
- (1) glomerular lesions;
- (2) renal vascular lesions, principally arteriolosclerosis
- (3) pyelonephritis, including necrotizing papillitis.

Diabetic complication: Nephropathy

- The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis.
- The glomerular capillary basement membranes are thickened along their entire length.
- **Diffuse mesangial sclerosis** consists of a diffuse increase in mesangial matrix along with mesangial cell . When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema

Diabetic complication: Nephropathy

- **Nodular glomerulosclerosis** : ball-like deposits of a laminated matrix situated in the periphery of the glomerulus . These nodules are PAS-positive . This distinctive change has been called the **Kimmelstiel-Wilson lesion.**
- Nodular glomerulosclerosis is encountered in approximately 15% to 30% of persons with long-term diabetes. It is essentially pathognomonic of diabetes.
- Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular-appearing cortical surface


Diabetic nephropathy
nodular lesion

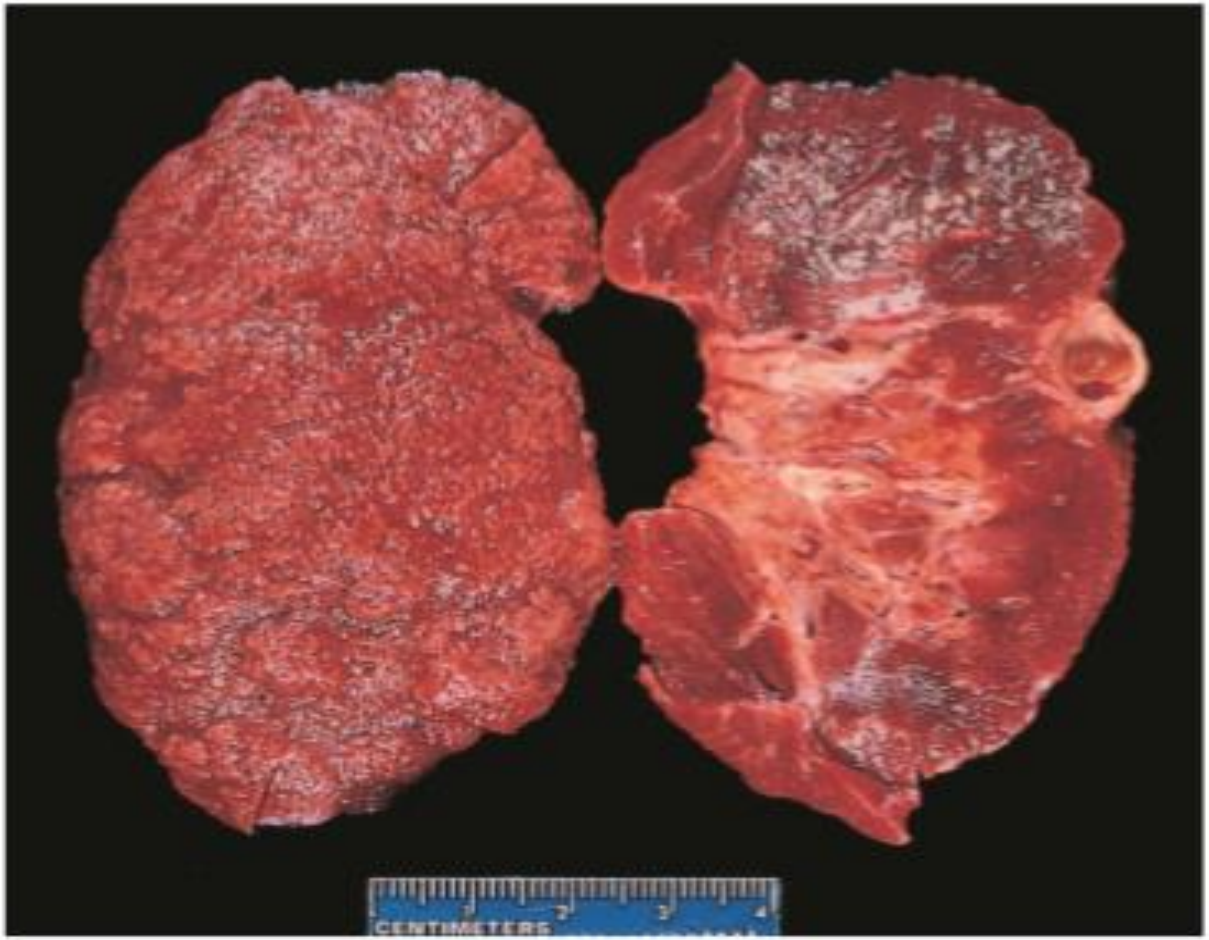


Fig. 20.31 Nephrosclerosis in a patient with long-standing diabetes. The bisected kidney demonstrates diffuse granular transformation of the surface *(left)* and marked thinning of the cortex *(right)*. Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst *(far right)*.

Diabetic complication: Nephropathy

- Pyelonephritis is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to involve the tubules. Both the acute and chronic forms of this disease occur in nondiabetics as well as in diabetics are more common in individuals with diabetes, and once affected, diabetics also tend to have more severe involvement.
- One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics.

Ocular Complications of Diabetes.

- **The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.**
- Retinopathy, the most common pattern
- **The lesion in the retina takes two forms: **nonproliferative (background) retinopathy**

  **** proliferative retinopathy.**

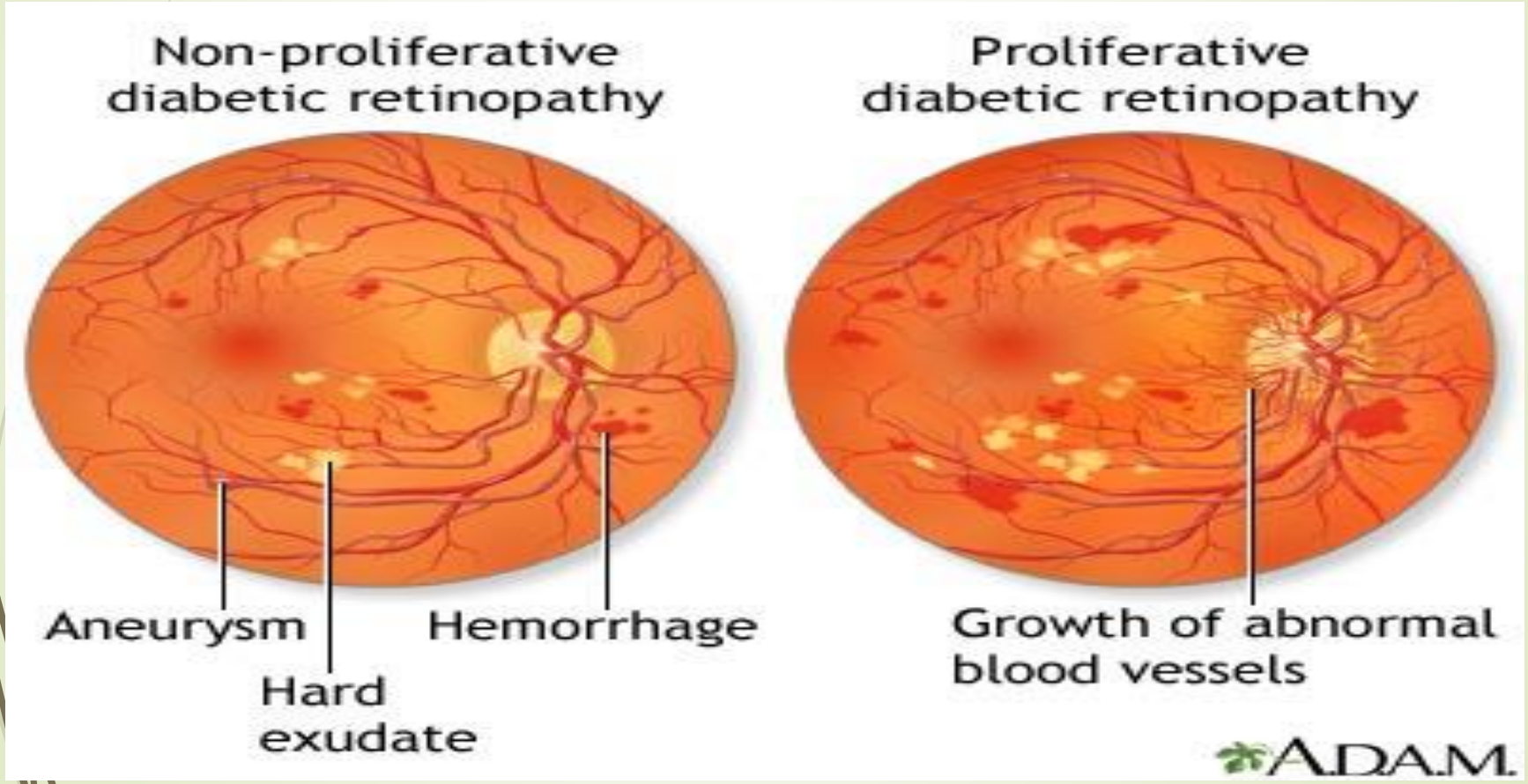
Nonproliferative retinopathy:

includes hemorrhages, retinal exudates, microaneurysms, venous dilations, edema, and, most importantly, thickening of the retinal capillaries (microangiopathy). The retinal exudates can be "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids) .

The microaneurysms are discrete saccular dilations of retinal choroidal capillaries that appear through the ophthalmoscope as small red dots. .

Proliferative retinopathy is a process of neovascularization and fibrosis.

- This lesion leads to serious consequences, including blindness, especially if it involves the macula and retinal detachment


Non-proliferative diabetic retinopathy
Proliferative diabetic retinopathy
Aneurysm
Hard exudate
Hemorrhage
Growth of abnormal blood vessels
A.D.A.M.

Diabetic Neuropathy.

- The central and peripheral nervous systems are not spared by diabetes.
- The most frequent pattern of involvement is that of a peripheral, symmetric neuropathy of the lower extremities affecting both motor and sensory function, particularly the latter.
- Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop .
- **Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.**

- Diabetic patients have an enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis.
- Such infections cause about 5% of diabetes-related deaths.
- In a person with diabetic neuropathy, a trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death

Infections

- Bacterial and Fungal Infections Occur in Diabetic Hyperglycemia if Poorly Controlled
- Renal papillary necrosis may be a devastating complication of bladder infection.
- Mucormycosis: A dangerous infectious complication of poorly controlled diabetes is often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.

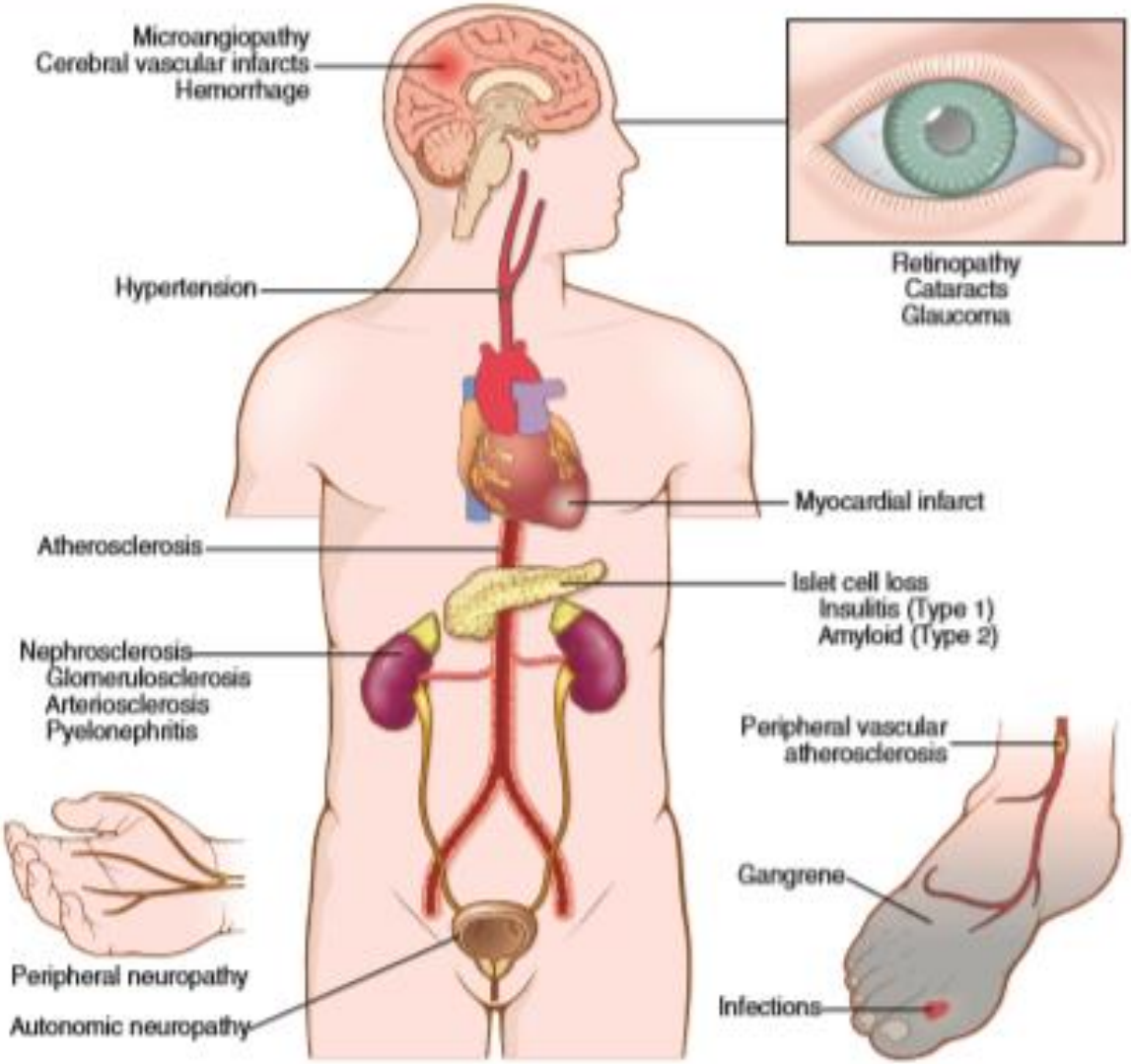


Fig. 20.25 Long-term complications of diabetes.

- For patients with type 1 diabetes, insulin replacement therapy is the mainstay of treatment, while nonpharmacologic approaches such as dietary restrictions and exercise (which improves insulin sensitivity) are often the "first line of defense" for type 2 diabetes.
- Most patients with type 2 diabetes eventually require therapeutic intervention to reduce hyperglycemia.
- Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin, also known as HbA1C, which is formed by nonenzymatic addition of glucose moieties to hemoglobin in red cells.
- Unlike blood glucose levels, HbA1C is a measure of glycemic control over long periods of time (2–3 months) and is relatively unaffected by day-to-day variations. The ADA recommends maintenance of HbA1C levels at less than 7% to reduce the risk for long-term complications.