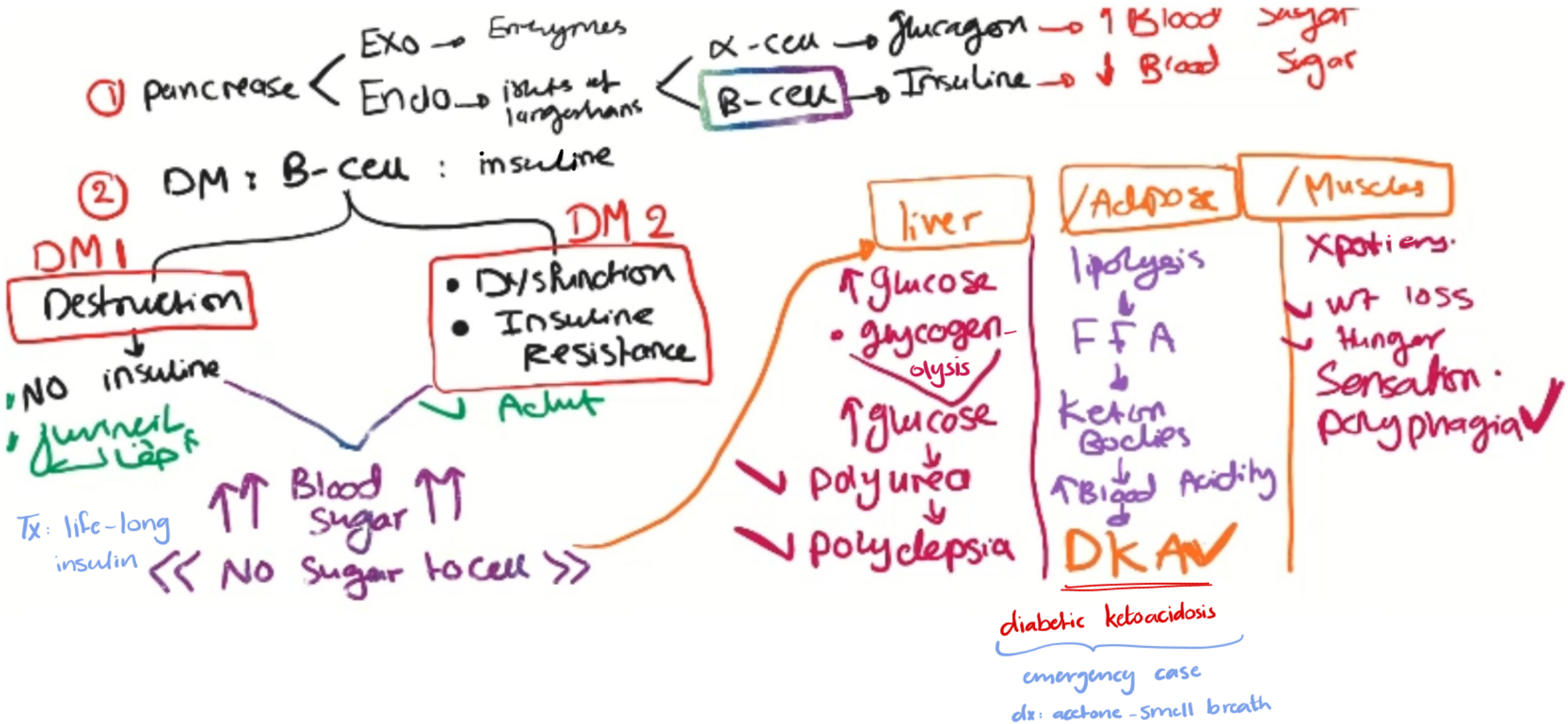
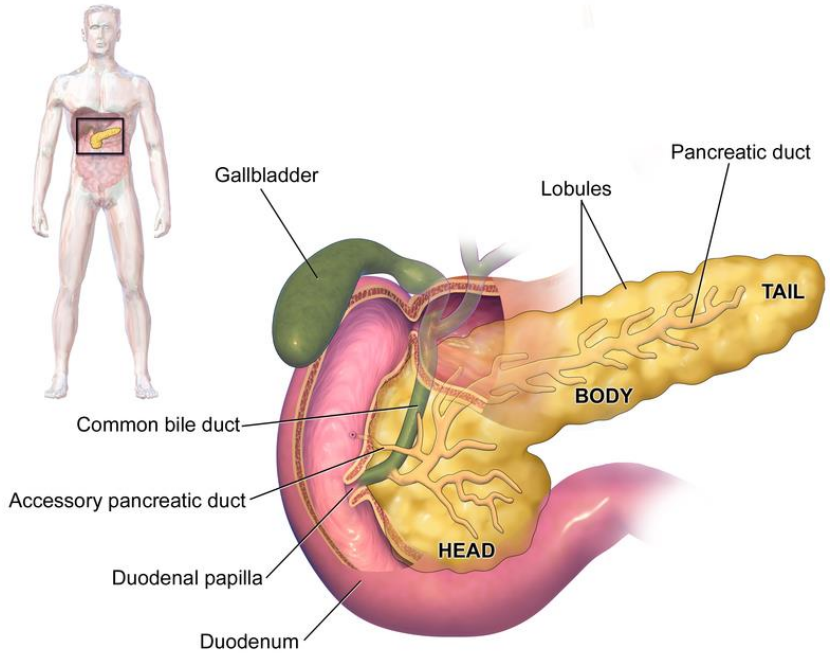
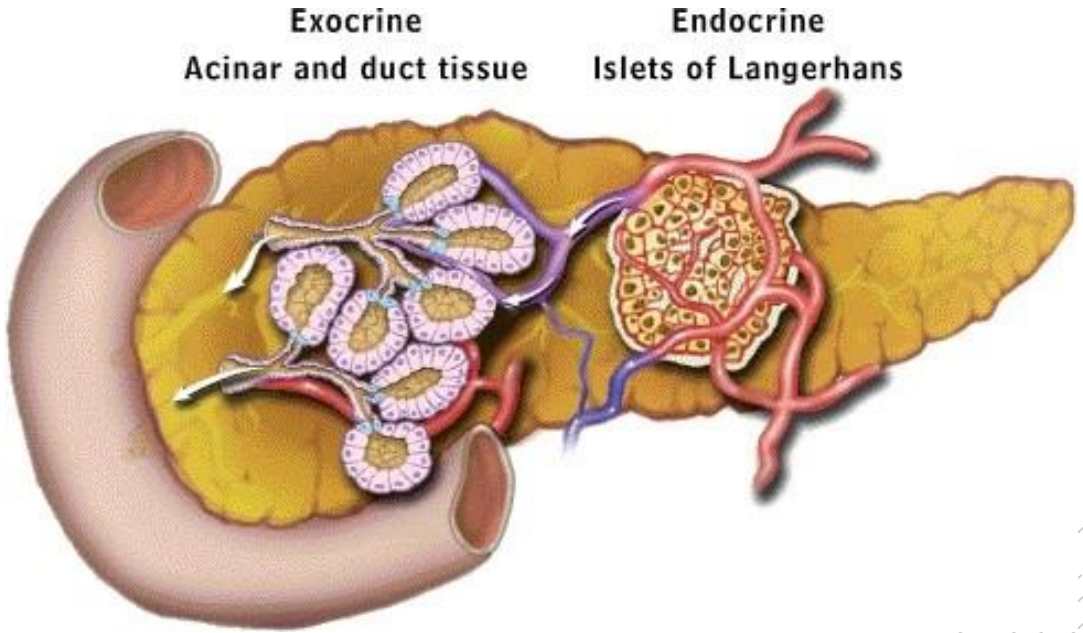
Diabetes mellitus


① pancrease
Exo → Enzymes
Endo → islets of langerhans
α-cell → glucagon → ↑ Blood sugar
B-cell → Insuline → ↓ Blood sugar
② DM : B-cell : insuline
DM1
Destruction
↓ insuline
NO insuline
Tx: life-long insulin
DM 2
• Dysfunction
• Insuline Resistance
↘ Adult
↑↑ Blood sugar ↑↑
<< No sugar to cell >>
liver
↑ glucose
• glycogen- olysis
↑ glucose
↘ polyurea
↘ polydepsia
/Adipose
lipolysis
FFA
Ketone Bodies
↑ Blood Acidity
DKA
/Muscles
Xpotiens.
↘ wt loss
↘ Hunger Sensation.
Polyphagia
diabetic ketoacidosis
emergency case
dx: acetone - smell breath

Pancreas. anatomy.



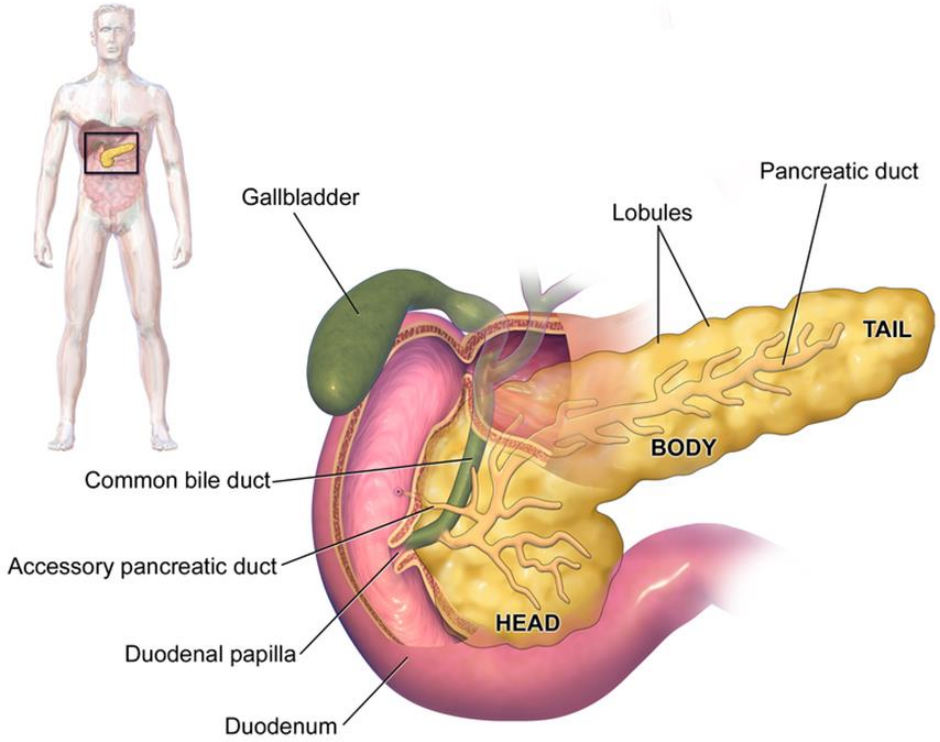


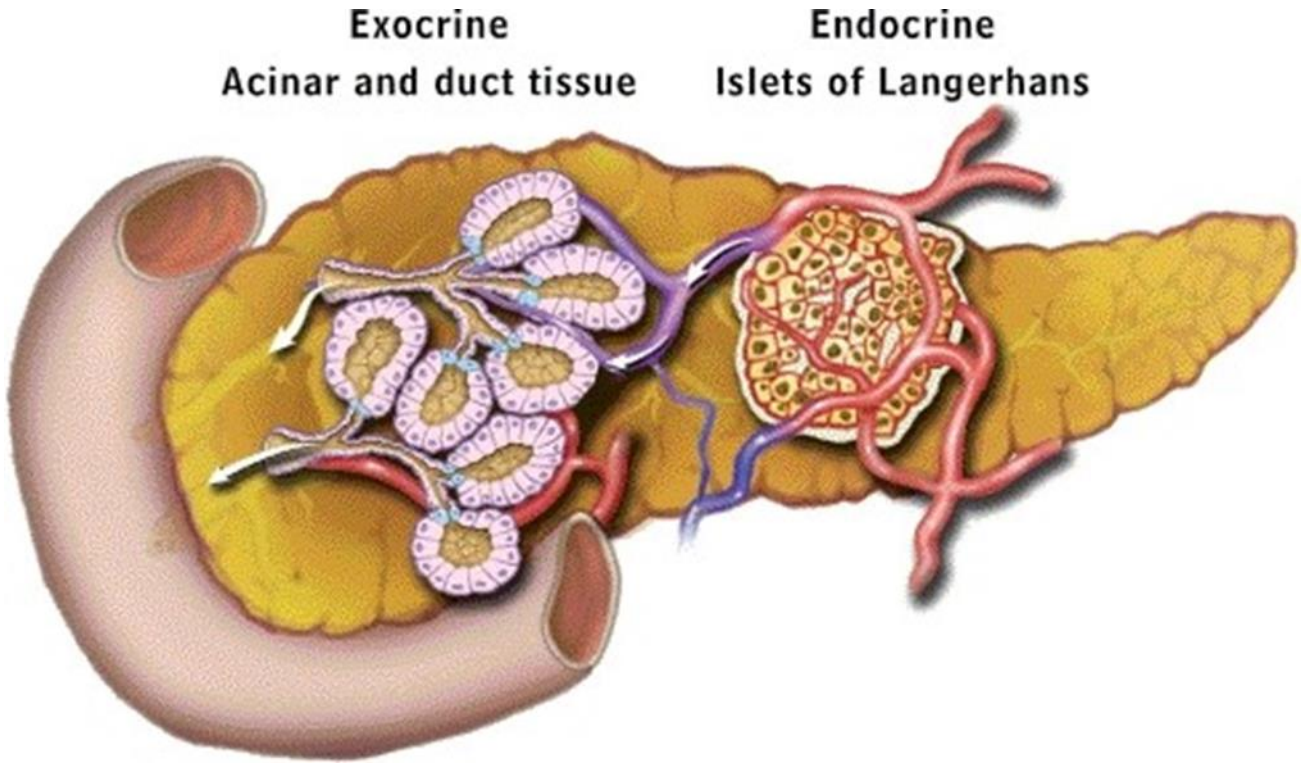
❖ Pancreas :

1. **Endocrine function:** islets of Langerhans

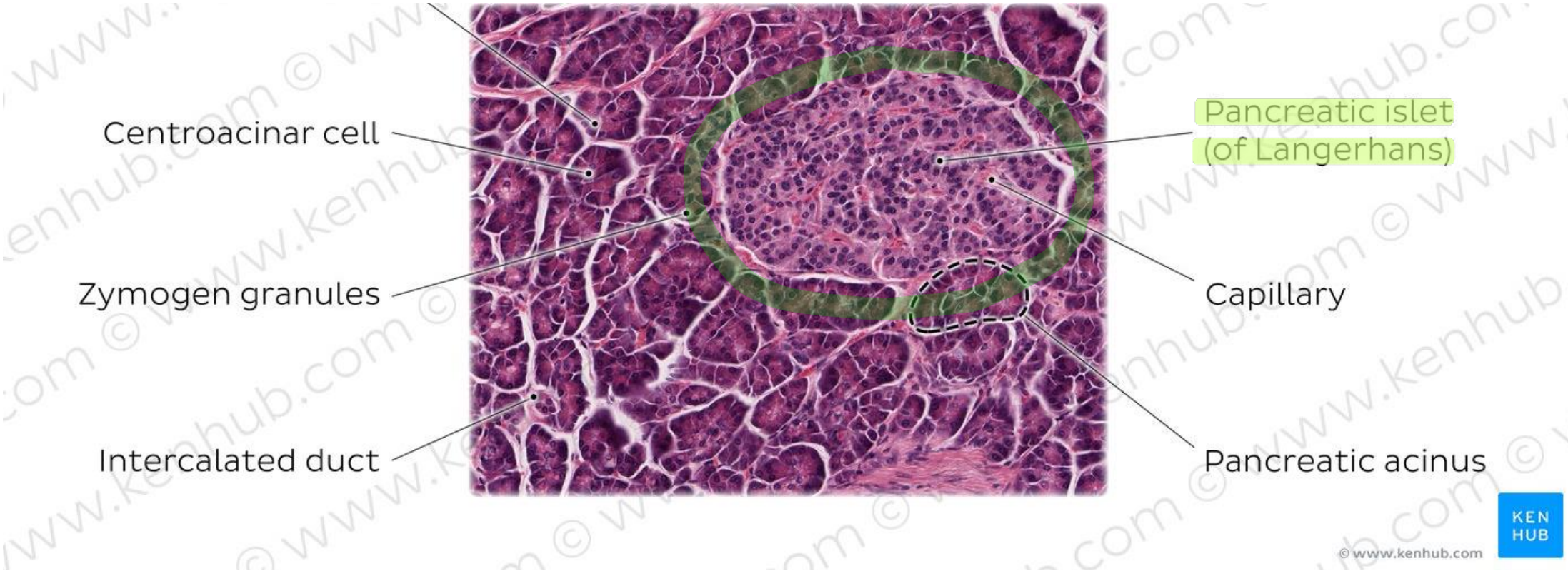
- **Alpha cells : glucagon : raise** blood sugar levels : **by stimulating the liver to convert stored glycogen into glucose**
- **Beta cells : insulin : lower** blood sugar levels : **by promoting the uptake of glucose from the bloodstream into cells**

2. **Exocrine function:** pancrease produces and releases **digestive enzymes** into the small intestine , such as amylase, lipase, and proteases, help break down carbohydrates, fats, and proteins respectively, aiding in the digestion and absorption of nutrients.





➢ Histology


Centroacinar cell
Zymogen granules
Intercalated duct
Pancreatic islet
(of Langerhans)
Capillary
Pancreatic acinus
© www.kenhub.com
KEN HUB

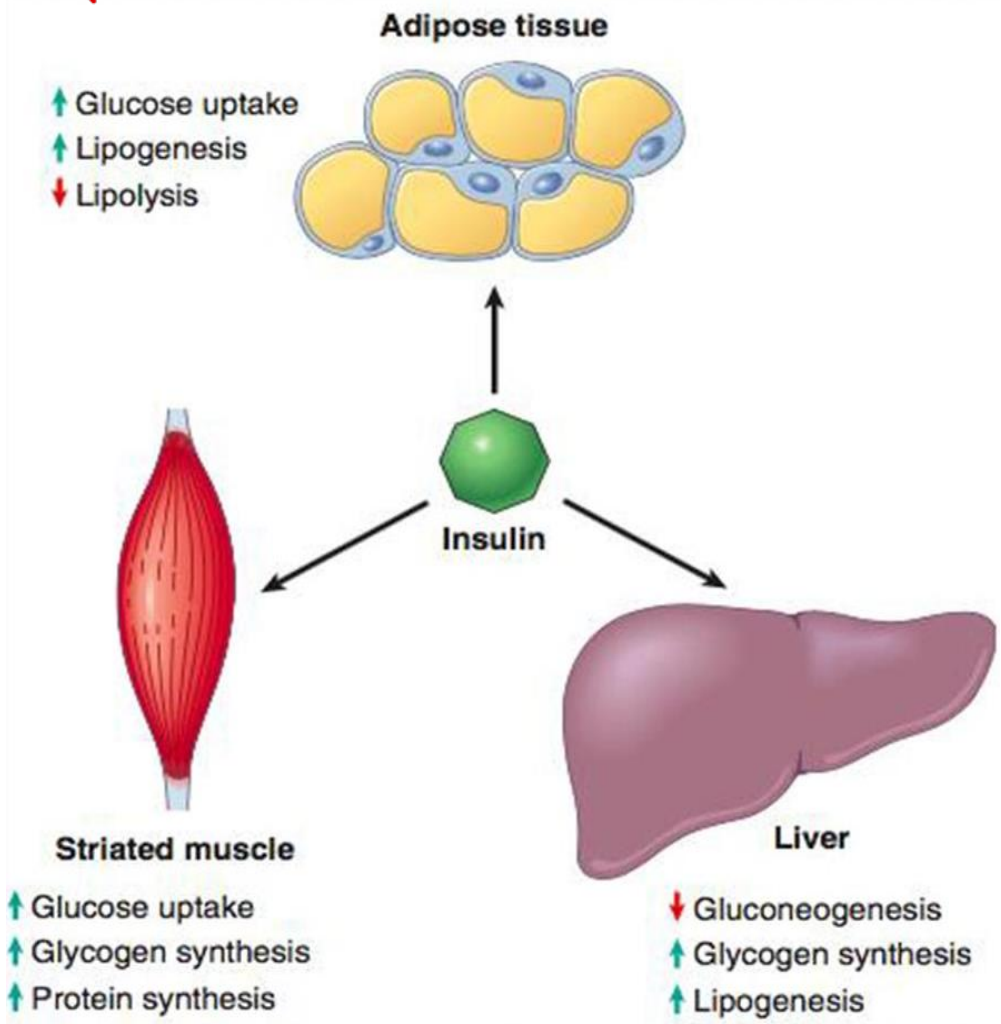


Fig. 20.21 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

Q: All processes are present in diabetic patient except:

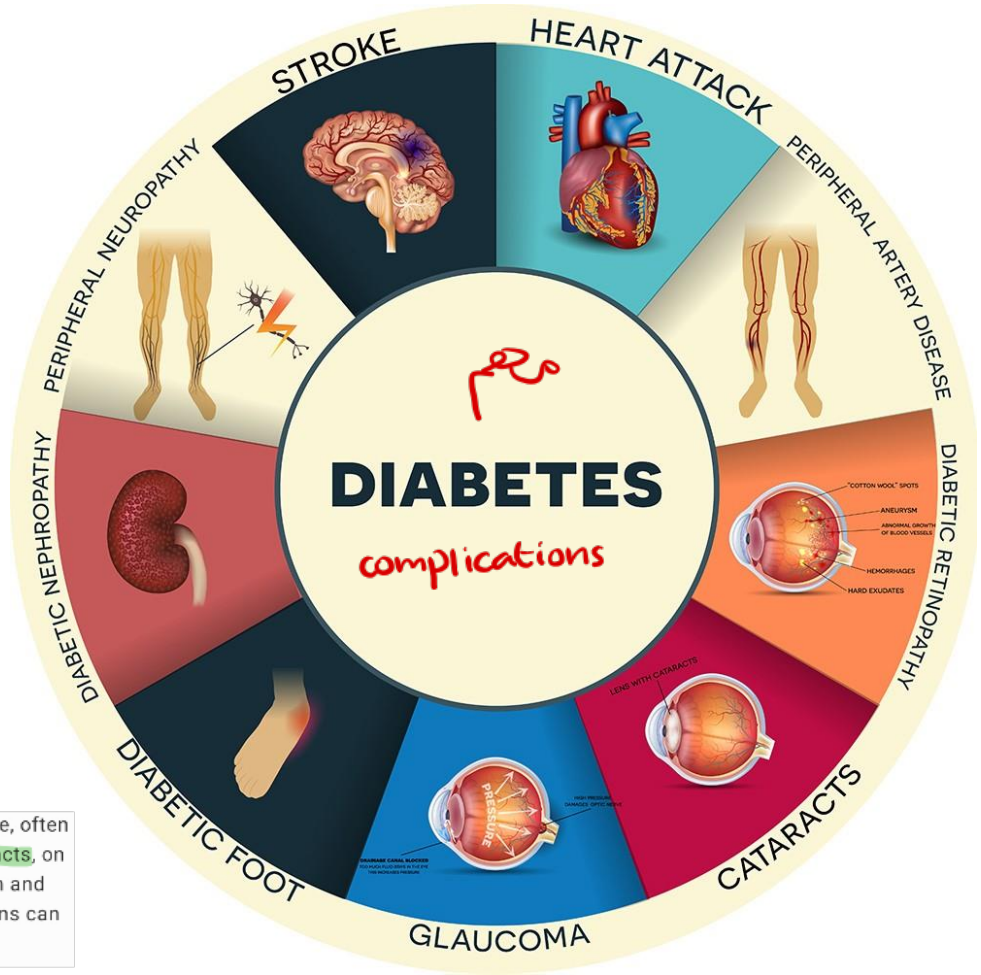
❖ Diabetes mellitus (DM) is a global health issue affecting children, adolescents, and adults.

❖ The WHO estimates that diabetes resulted in :

✓ 1.5 million deaths in 2012.

✓ **making it the 8th leading cause of death.**

✓ 2.2 million deaths worldwide were attributable to high blood glucose and the increased risks of cardiovascular disease and other associated complications (e.g. kidney failure),

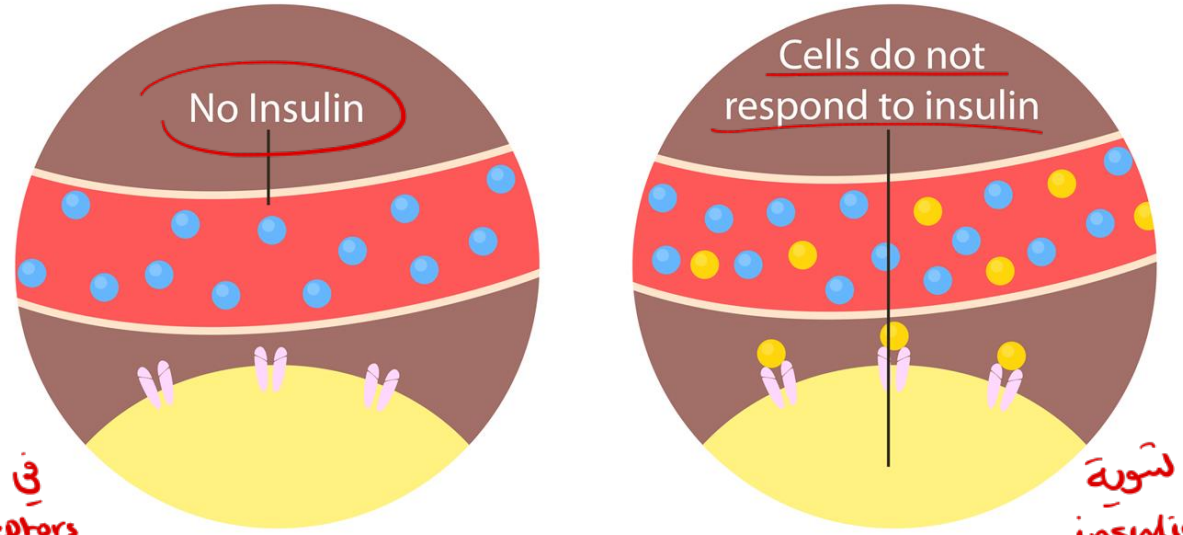


Glaucoma is a group of eye conditions that damage the optic nerve, often due to increased pressure in the eye, leading to vision loss. Cataracts, on the other hand, are clouding of the eye's lens, causing blurry vision and eventually leading to vision impairment if untreated. Both conditions can impact eyesight but have different causes and treatments.

Diabetes mellitus

group of metabolic disorders characterized by **hyperglycemia**

difference between the 2 types:
1. age group
2. mechanism



في receptors بس في insulin
↓ may progress to ketoacidosis coma

insulin بس resistant + hunger state in tissue + hyperglycemia in blood

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

نقط معرفة

❖ Type 1 diabetes (T1D)

- **Autoimmune disease** in which **islet destruction** is caused primarily by immune effector cells reacting against endogenous beta cell antigens.
- formerly known as **juvenile diabetes.**
- Most patients with type 1 diabetes **depend on exogenous insulin for survival**
- without insulin they develop serious metabolic complications such as **ketoacidosis and coma.**

❖ Pathogenesis

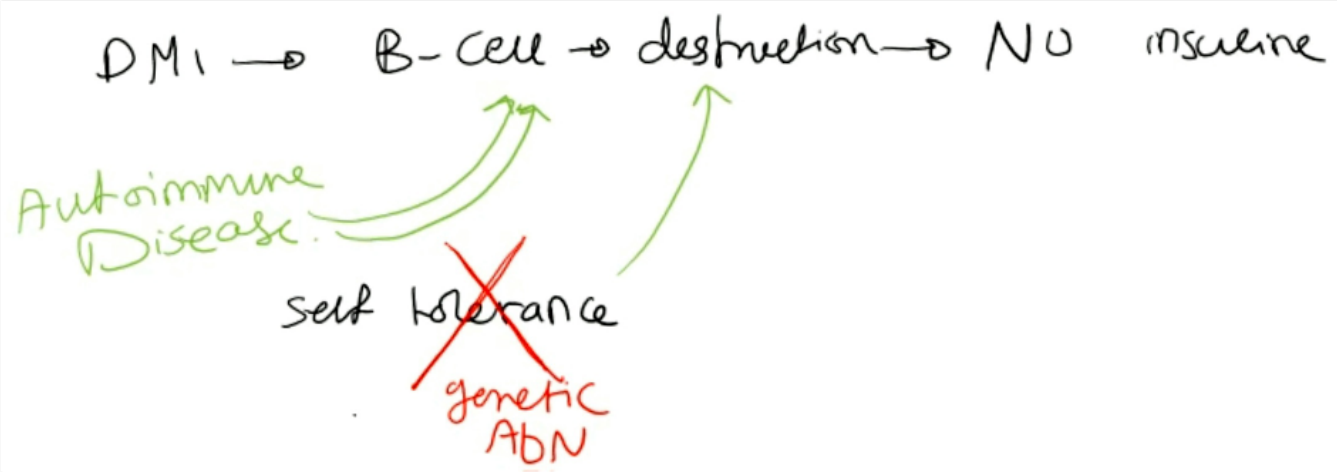
- the pathogenesis of type 1 diabetes involves:

✓ **Genetic** susceptibility: **HLA-DR3, or DR4**, **failure of self-tolerance in T cells specific for beta cell antigens.**

✓ **Environmental** factors: infection

- All lead to : production of **autoantibodies** against a variety of beta cell antigens, including insulin and the beta cell enzyme glutamic acid decarboxylase.

▷ complete destruction of B-cells & complete def. of insulin



❖ Type 2 diabetes (T2D)

- 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)**.

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

SYMPTOMS OF TYPE 1 DIABETES

due to polyurea

	Abnormal thirst and dry mouth
	Frequent urination ← glucosurca, ketonurca
	Lack of energy, fatigue
	Blurred vision
	Constant hunger — elevation of AA and FA
	Sudden weight loss — due to catabolism and lipolysis
	Bed-wetting

SYMPTOMS OF TYPE 2 DIABETES

تقريبًا نفس الأعراض

	Excessive thirst and dry mouth
	Frequent and abundant urination
	Lack of energy, extreme tiredness
	Blurred vision
	Recurrent fungal infections of the skin esp. between toes
	Slow healing wounds due to microvascular disease ↑↑ bacterial multiplication due to ↑↑ glucose
	Tingling or numbness in hands and feet due to neuropathy

❖ 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 where insulin resistance manifests as follows:

✓ Failure to inhibit endogenous glucose production (gluconeogenesis) in the **liver**, which contributes to high fasting blood glucose levels .

✓ Abnormally low glucose uptake and glycogen synthesis in **skeletal muscle** following a meal, which contributes to a high postprandial blood glucose level.

✓ Failure to inhibit hormone-sensitive lipase in **adipose tissue**, leading to excess circulating free fatty acids (FFAs), which, exacerbates the state of insulin resistance

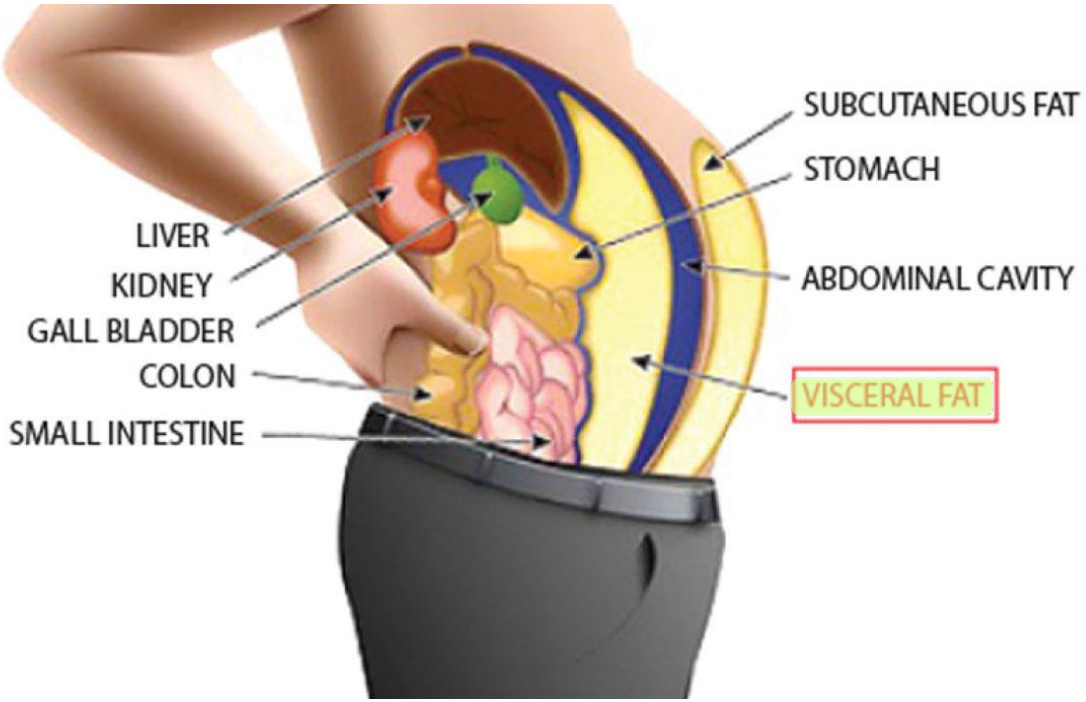
* Phenotype of insulin resistant patients :

- central obesity , visceral obesity
- darkened back of neck
- acne
- Hairsutism (excess facial hair)
- weight gain
- menestrual irregularity
- polycystic ovarian syndrome

❖ Obesity and Insulin Resistance

- The association of obesity with type 2 diabetes has been recognized for decades,
- with **visceral obesity** being common in a majority of affected patients.

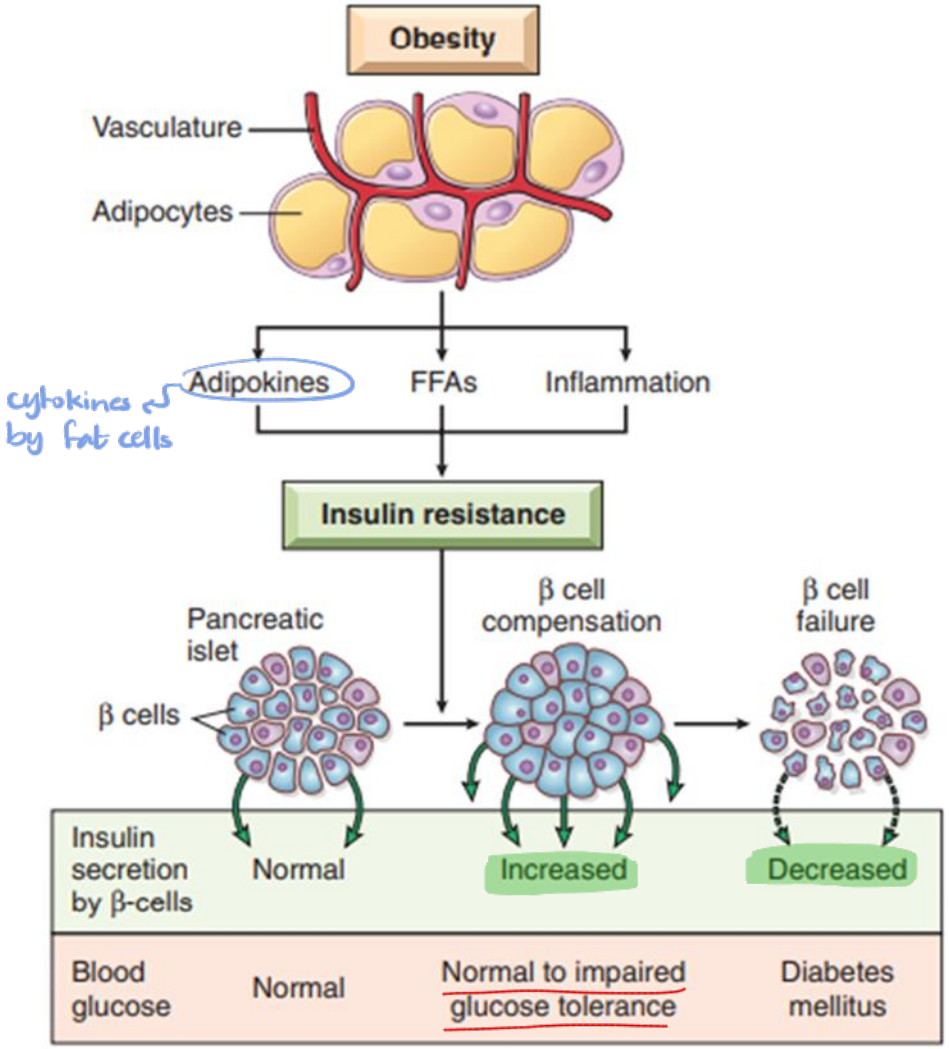
↳ excess adipose tissue ← ↑↑ adipokines, ↑↑ FFA, ↑↑ inf. mediators



❖ Obesity can adversely impact insulin sensitivity in numerous ways

1. Excess FFAs.
2. Adipokines.
3. Inflammation:

inflammatory milieu (mediated by proinflammatory cytokines that are secreted in response to excess nutrients such as FFAs) results in both peripheral insulin resistance and beta cell dysfunction



❖ Beta Cell Dysfunction

- beta cell dysfunction is an essential component in the development of **overt diabetes.**
- Several mechanisms have been implicated:

✓ **Excess free fatty acids** that compromise beta cell function and **attenuate insulin release (**lipotoxicity**)**.

✓ **Chronic hyperglycemia** (glucotoxicity) .

❖ MORPHOLOGY

- Reduction in the number and size of islets.
- Leukocytic infiltrates in the islets.
- **Amyloid deposition** within islets in type 2 diabetes.

Normal Sites for Amyloid Deposition:

- Brain: Alzheimer's disease can involve amyloid plaques.
- Heart: Amyloid can deposit in the heart, leading to cardiomyopathy.
- Kidneys: Amyloidosis can affect the kidneys, causing proteinuria and renal failure.
- Liver: Hepatic amyloidosis can occur but is usually asymptomatic.
- Spleen: Amyloid deposits can occur in the spleen.

Diseases Associated with Amyloidosis:

- Alzheimer's Disease: Amyloid plaques in the brain are a hallmark of Alzheimer's.
- Cardiac Amyloidosis: Amyloid deposits in the heart can lead to heart failure.
- Renal Amyloidosis: Kidney damage and dysfunction due to amyloid deposition.
- Primary Systemic Amyloidosis (AL Amyloidosis): Associated with plasma cell disorders like multiple myeloma.
- Secondary Amyloidosis (AA Amyloidosis): Can result from chronic inflammatory conditions like rheumatoid arthritis.
- Hereditary Amyloidosis: Inherited genetic mutations lead to amyloid deposition in various organs.

amyloid is a misfolded protein

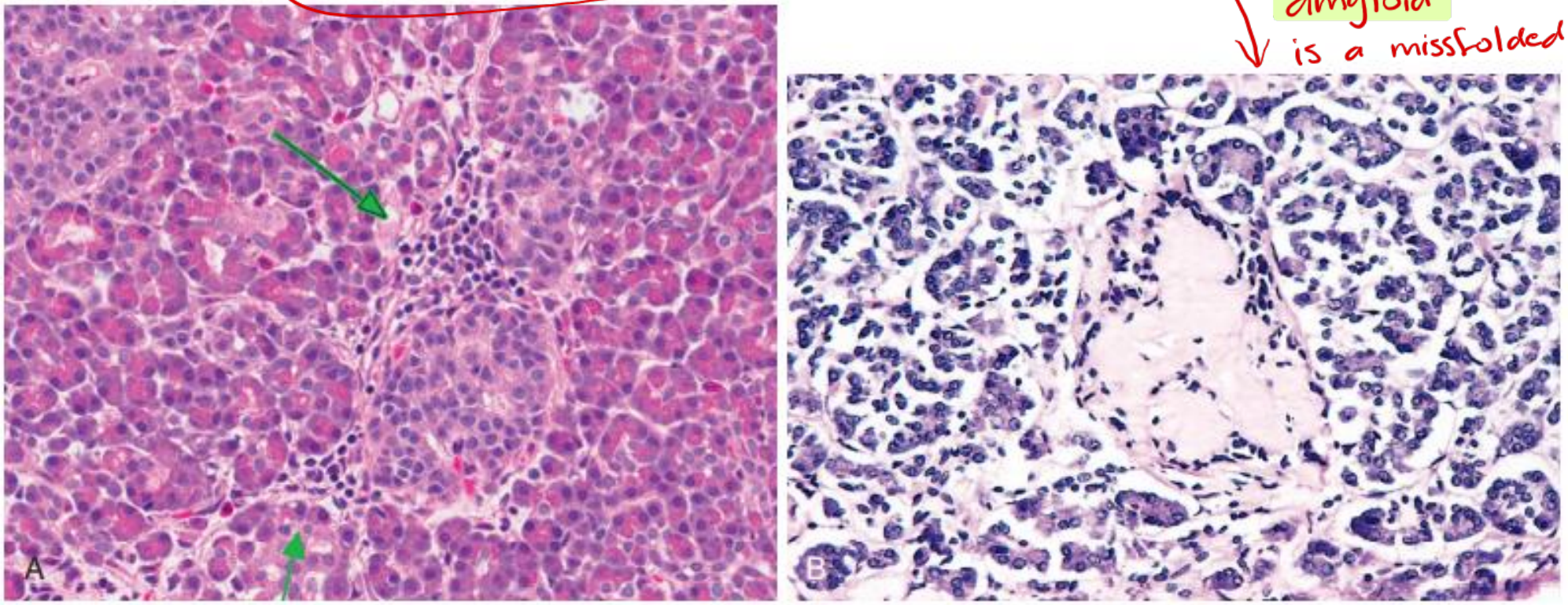
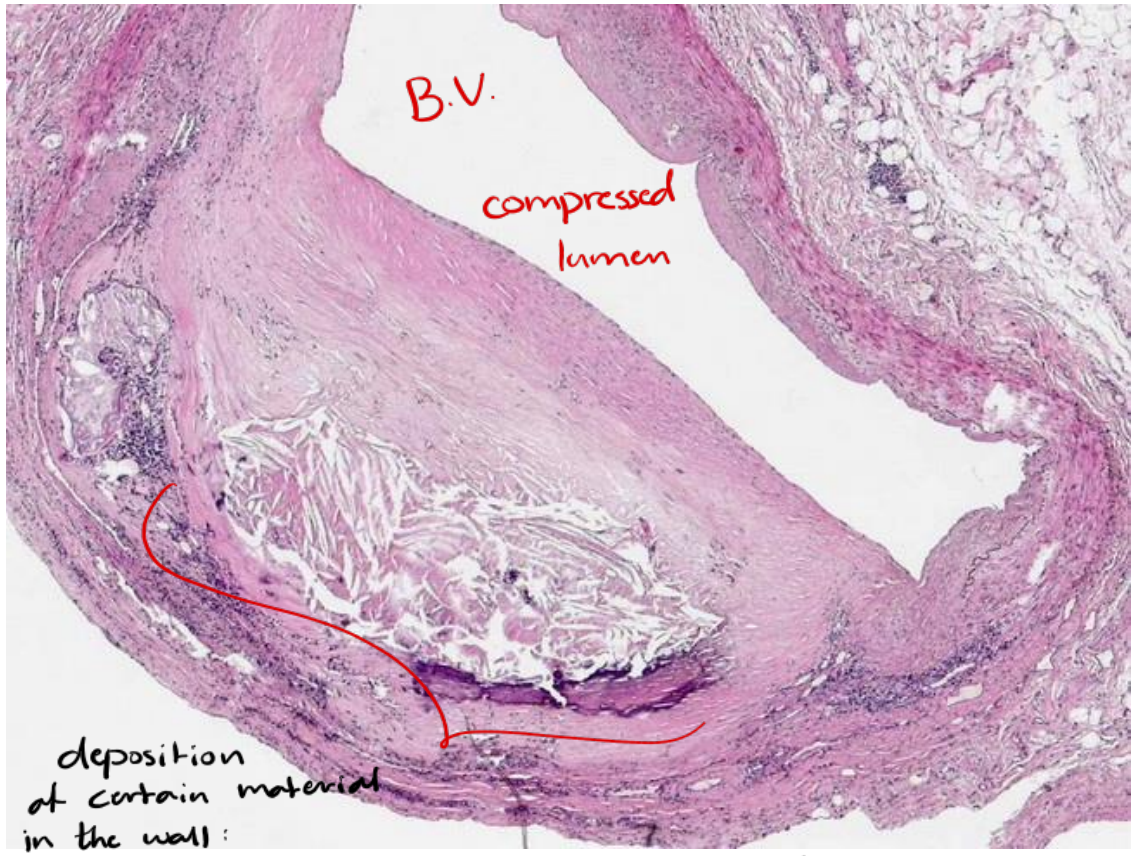


Fig. 20.26 (A) Autoimmune insulitis in a human pancreatic explant. Arrows point to inflammation surrounding islet of Langerhans, while the surrounding acinar structures are essentially normal. *(Photograph provided by Dr. Martha Campbell-Thompson, JDRF Network for Pancreatic Organ Donors, University of Florida., Gainesville, Florida.)* (B) Amyloidosis of a pancreatic islet in type 2 diabetes. Amyloidosis typically is observed late in the natural history of this form of diabetes, with islet inflammation noted at earlier observations.

* Complications on B.V. due to effect of glucose < microvascular → retina , kidney
macrovascular → coronary arteries in heart

- **Diabetic macrovascular disease :**
- The hallmark of diabetic macrovascular disease is accelerated **atherosclerosis.**
- **Hyaline arteriolosclerosis.**



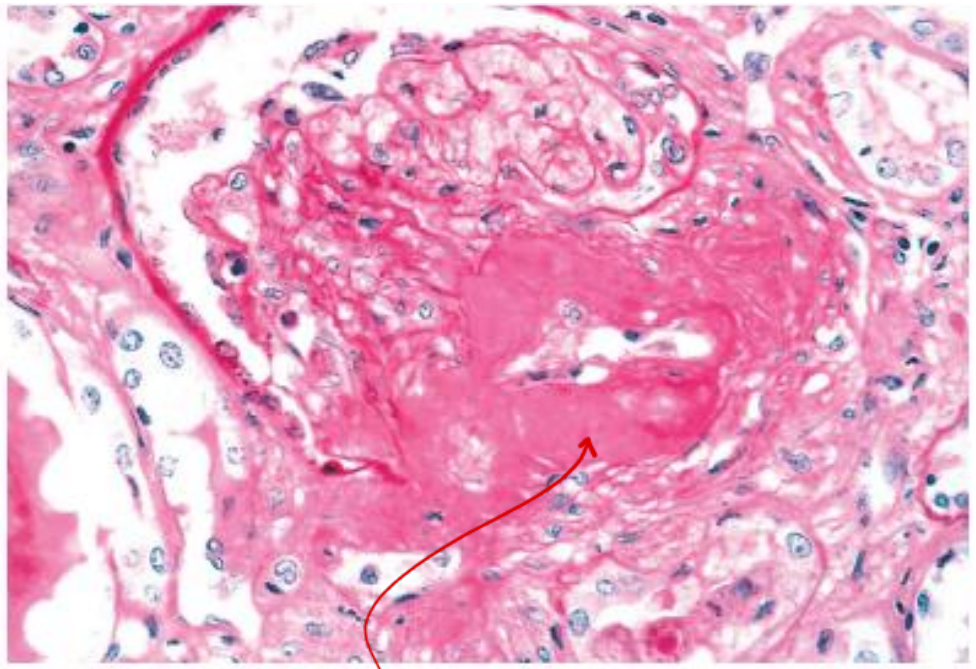


Fig. 20.27 Severe renal hyaline arteriolosclerosis in a periodic acid–Schiff stained specimen. Note the markedly thickened, tortuous afferent arteriole. The amorphous nature of the thickened vascular wall is evident. *(Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Science Center, San Antonio, Texas.)*

❖ Mechanisms for micro or macro vascular disease in diabetes

Glycation is a process where sugars (such as glucose) bind to proteins or lipids without the controlling action of enzymes.

❖ pathologic effects of advanced glycation end product accumulation:

✓ impaired vasodilatory response attributable to **nitric oxide inhibition**,. V.D.

✓ **smooth muscle cell dysfunction.**

✓ overproduction of **endothelial growth factors.**

✓ **chronic inflammation**

❖ Diabetic nephropathy:

- Glomerular lesions.
- Renal vascular lesions, principally arteriolosclerosis.

Renal cortex showing thickening of tubular basement membranes .

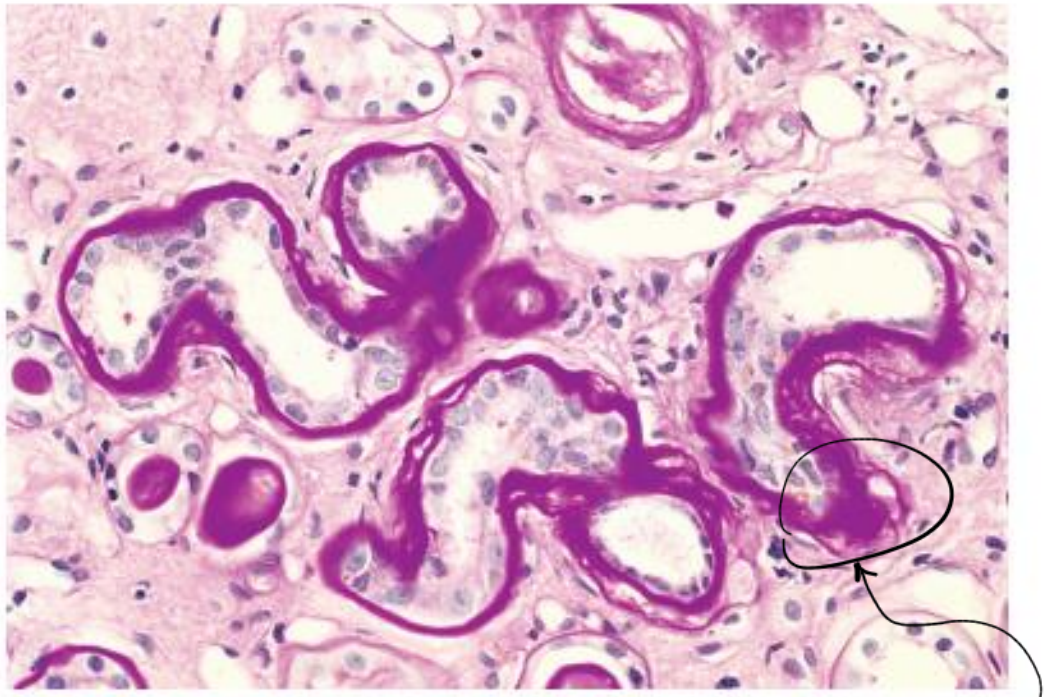


Fig. 20.28 Renal cortex showing thickening of tubular basement membranes in a specimen from a diabetic patient. (Periodic acid–Schiff stain.)

Nodular glomerulosclerosis

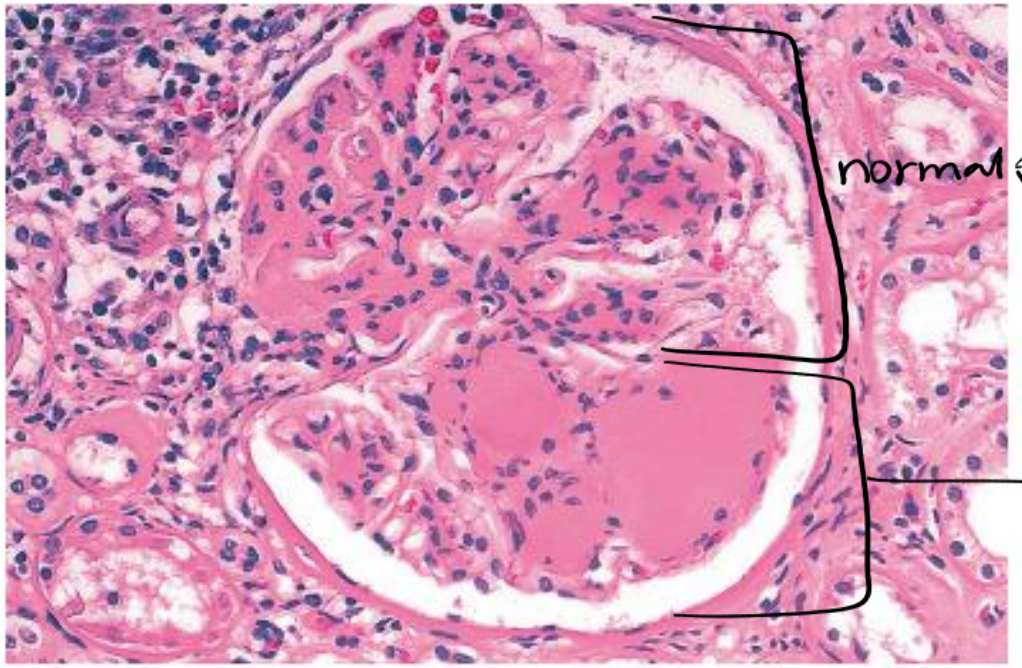


Fig. 20.30 Nodular glomerulosclerosis in a renal specimen from a patient with long-standing diabetes. *(Courtesy of Dr. Lisa Yerian, Department of Pathology, University of Chicago, Chicago, Illinois.)*

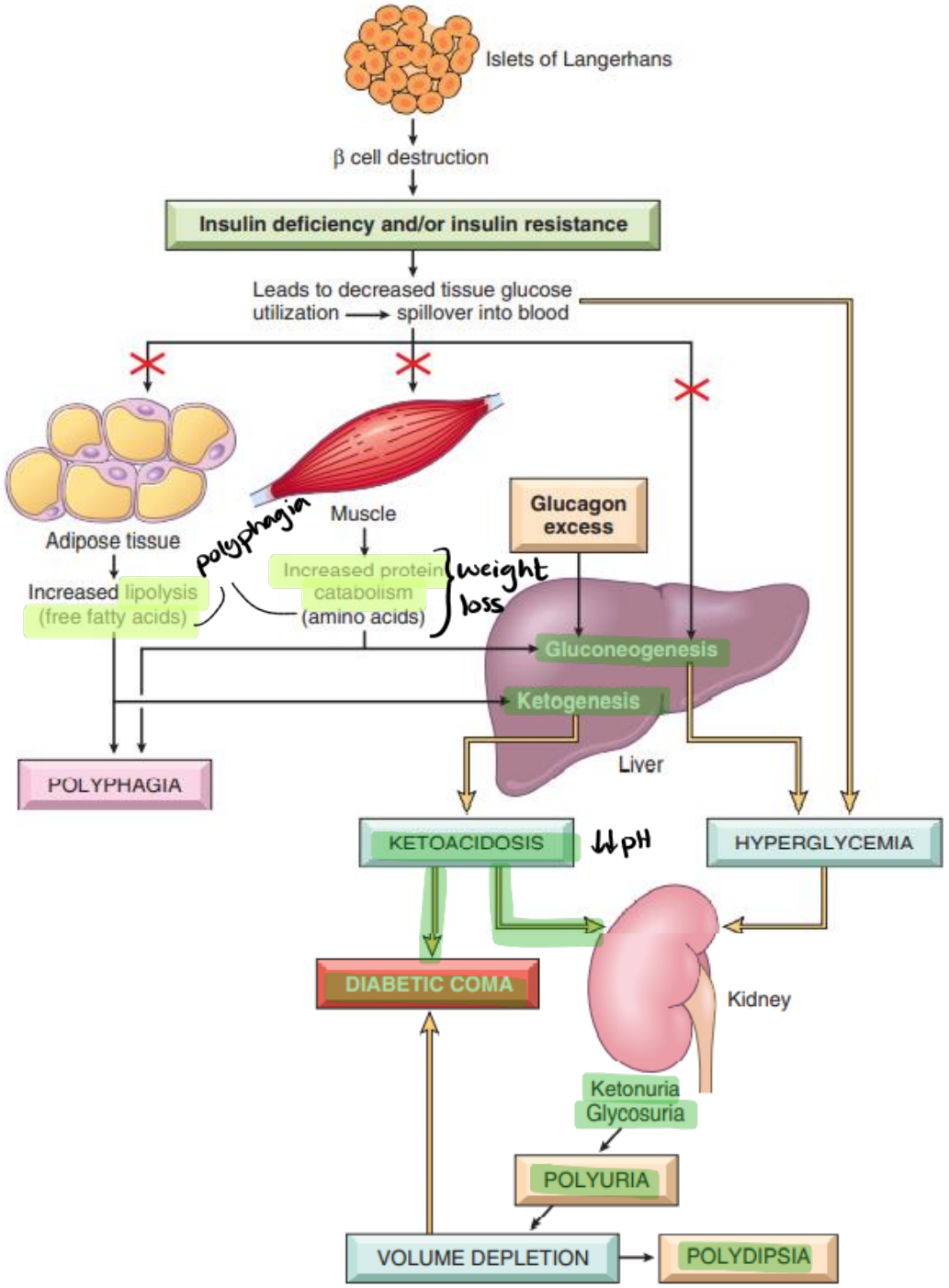
❖ Metabolic Complications:

- Acute Metabolic Complications of Diabetes.
- Chronic Complications of Diabetes.

❖ **Acute Metabolic Complications:**

❖ **classic triad of diabetes:**

- **Polyuria.**
- **polydipsia.**
- **Polyphagia.**



❖ Chronic Complications of Diabetes :

➢ damage induced in :

✓ **Large- and medium-sized muscular arteries**

(diabetic macrovascular disease) :

causes accelerated **atherosclerosis** among diabetics, resulting in increased **myocardial infarction**, **stroke**, and **lower-extremity ischemia**

✓**Small-vessels**

(diabetic microvascular disease)

The effects of microvascular disease are most profound in the **retina**, **kidneys**, and **peripheral nerves**, resulting in:

- Diabetic retinopathy
- Nephropathy
- Neuropathy

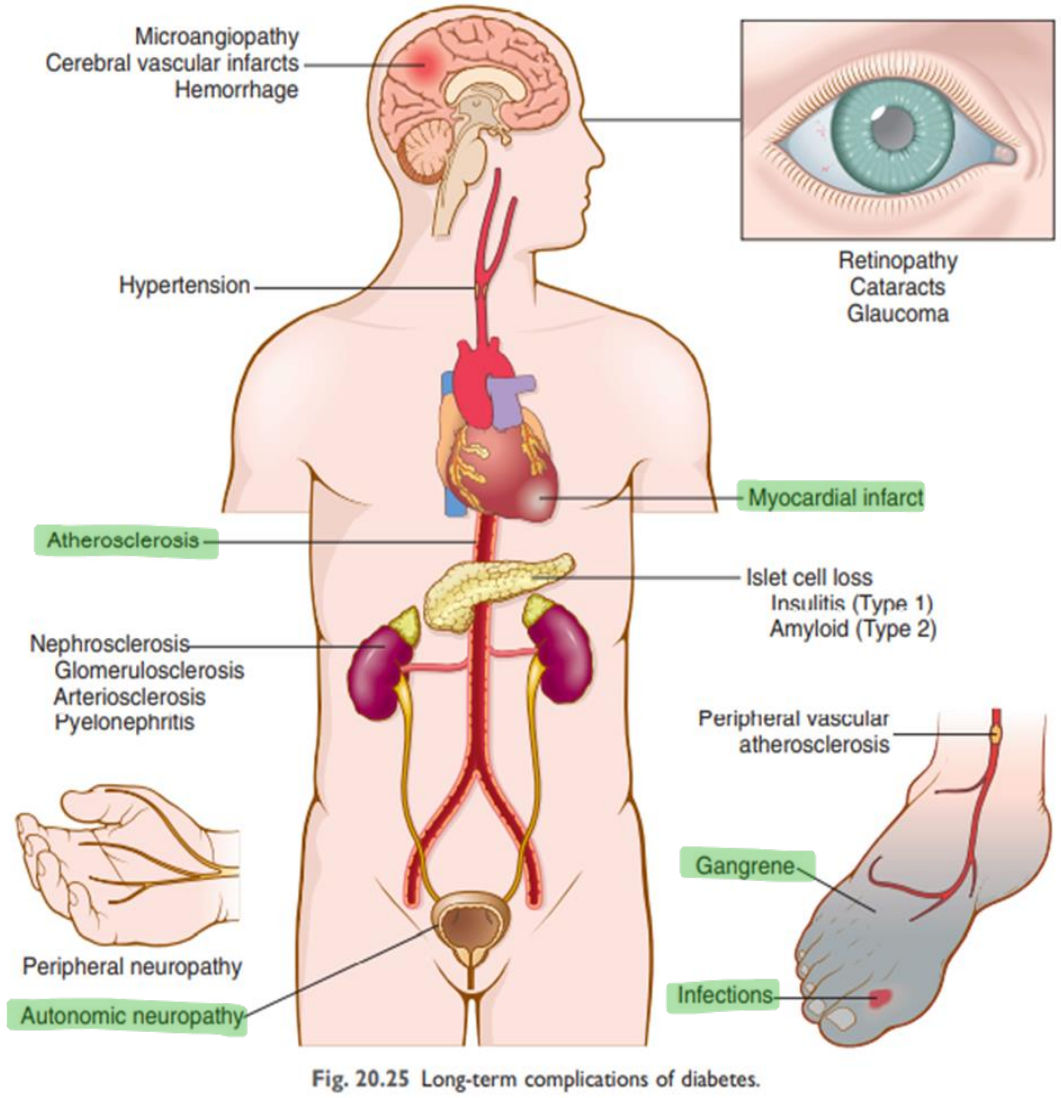


Fig. 20.25 Long-term complications of diabetes.

❖ Diabetic retinopathy

- Features include:

✓ advanced proliferative retinopathy.

✓ retinal hemorrhages.

✓ Exudates.

✓ neovascularization (friable) due to ischemia

✓ tractional retinal detachment retina بتتحرك ال من مكانها