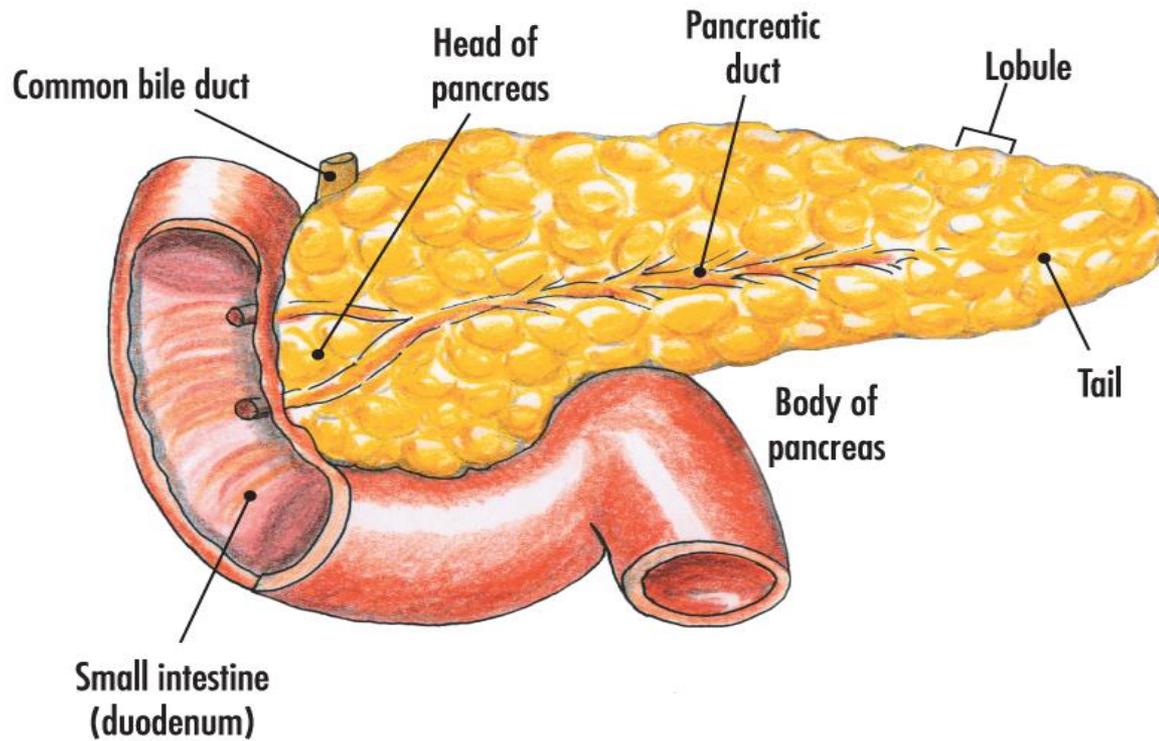


# Endocrine 2019 : Diabetes Mellitus

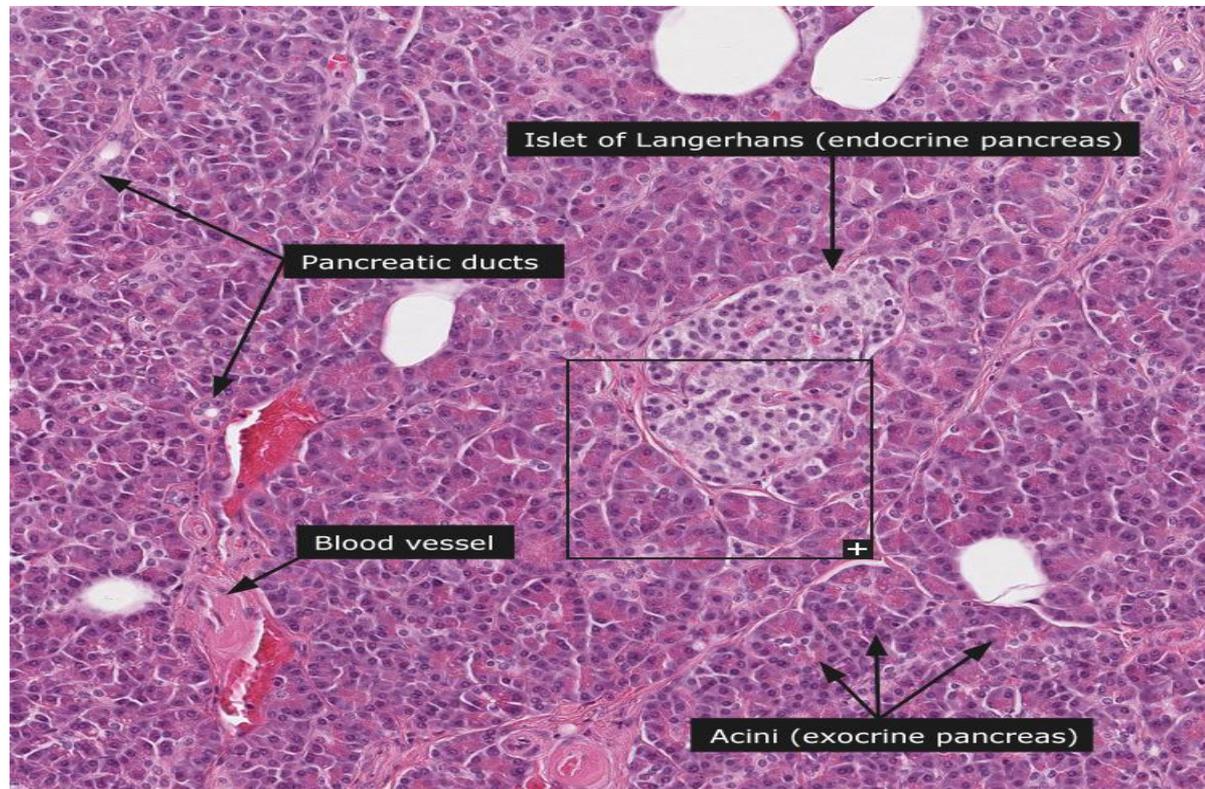
Dr Heyam Awad

FRCPath

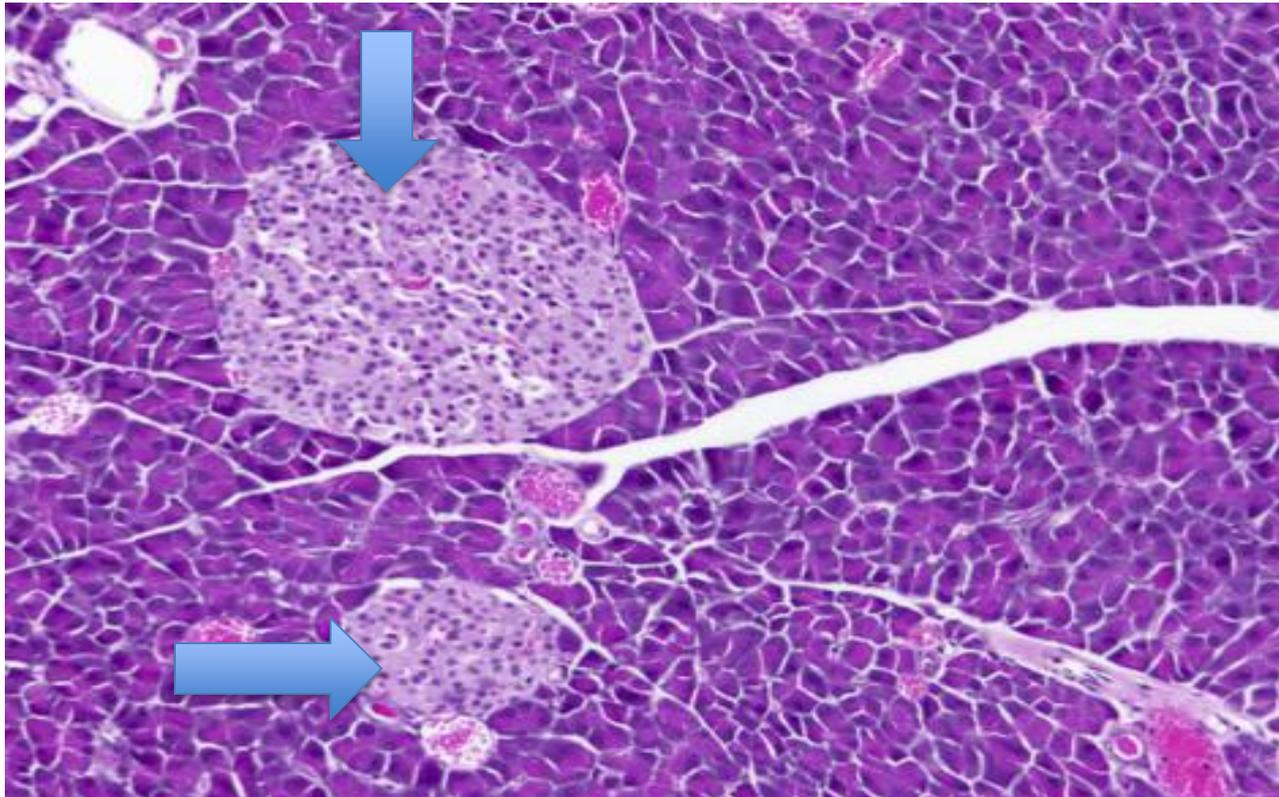
# The pancreas



**Exocrine pancreas**= glands and ducts that secrete enzymes, mainly for digestion.  
**Endocrine pancreas**= Islets of Langerhans (clusters of endocrine cells) that secrete hormones.



There are around one million Islets (arrows) in the pancreas!



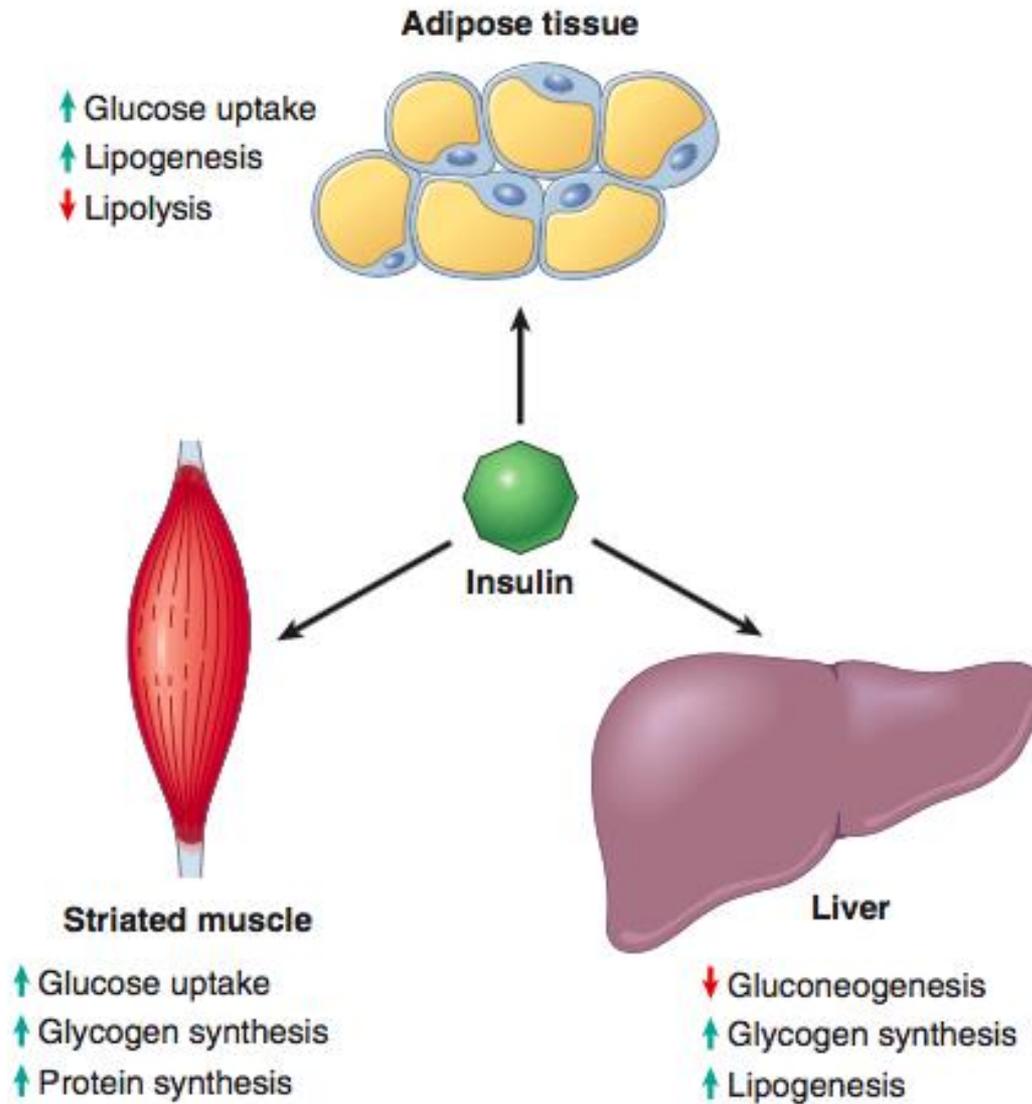
- Islets of Langerhans contain several types of cells, the most important are alpha and beta
- Alpha cells secrete glucagon
- Beta cells secrete insulin
- Delta cells secrete somatostatin, which suppresses both insulin and glucagon.

# Diabetes Mellitus (DM)

- DM IS A **GROUP** OF METABOLIC DISORDERS SHARING HYPERGLYCEMIA.
- Blood glucose levels normally are maintained in a very narrow range, usually 70 to 120 mg/dL.
- This is maintained by the balance between insulin and glucagon

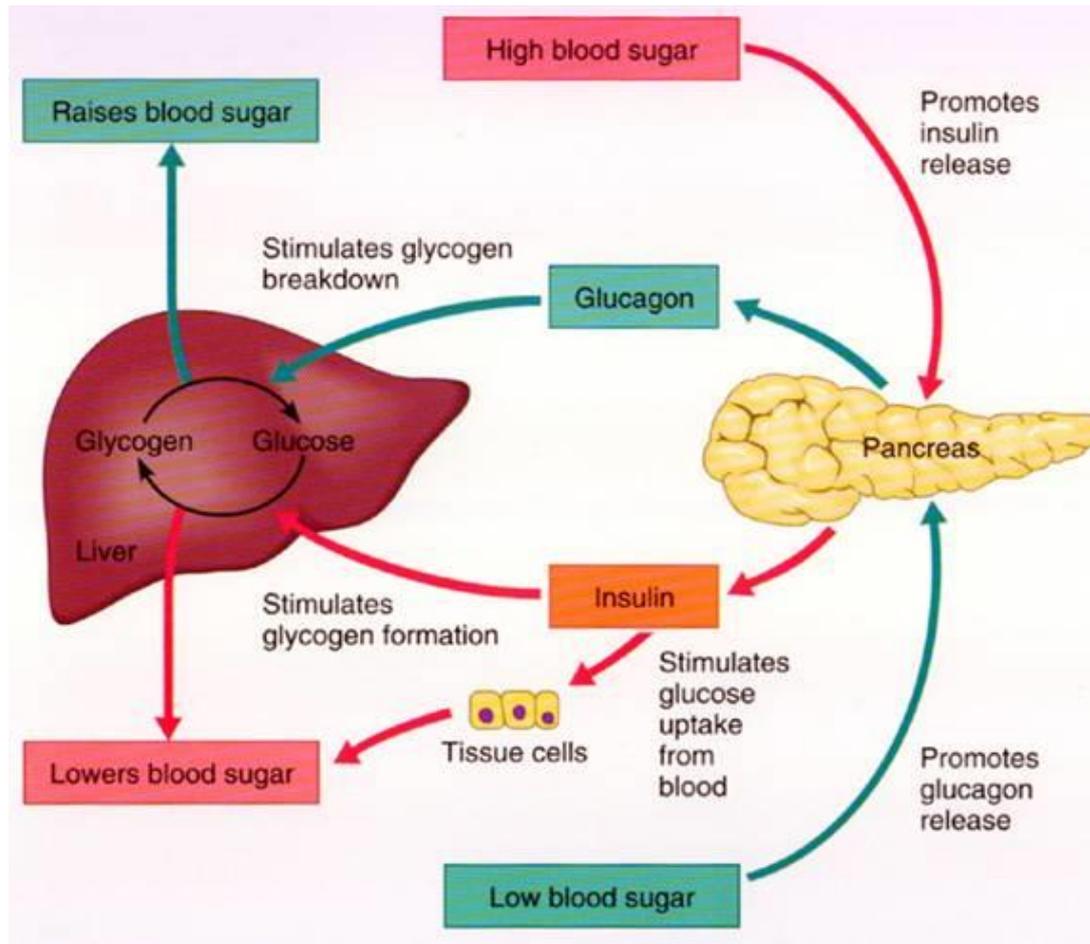
# Insulin effect

- Increase uptake of glucose by striated muscle and adipocytes.
- Insulin has anabolic effect on lipid, protein and glycogen.
- Insulin reduces production of glucose from liver.



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

# Insulin effect



# Criteria to diagnose DM

- According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diagnostic criteria for diabetes include the following
- 1. 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 hyperglycaemic signs 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 haemoglobin (HbA1C) level greater than or equal to 6.5

# PREDIABETES

- = impaired glucose tolerance.
- elevated blood sugar that does not reach the criteria for diagnosis of diabetes
- persons with prediabetes have an elevated risk for development of frank diabetes.

# Criteria to diagnose prediabetes

- Impaired glucose tolerance (prediabetes) is defined as
  - 1. A fasting plasma glucose between 100 and 125 mg/dL , 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

- Up to one-fourth of individuals with impaired glucose tolerance will develop diabetes in the next 5 years.

# NOTE

Many acute stresses, such as severe infections, burns or trauma, can lead to transient hyperglycemia due to secretion of hormones like catecholamine and cortisol that oppose the action of insulin. **The diagnosis of diabetes requires persistence of hyperglycemia following resolution of the acute stress.**

# Classification of DM

- Type 1... **absolute** insulin deficiency due to **destruction** of the islets by **autoimmune** mechanisms
- Type 2.. **Relative** insulin deficiency .... Peripheral **resistance** to insulin and **inadequate compensatory response** of insulin secretion.
- Other rare causes.. See next slide

# Other rare causes

1) Genetic defects of beta cell function.

-maturity onset diabetes of the young= MODY  
due to several mutations.

-insulin gene mutations.

-defects in proinsulin conversion

2) Genetic defects in insulin action.. Insulin  
receptor mutations.

3) Gestational diabetes.. During pregnancy

- 4)exocrine pancreatic defects: chronic pancreatitis, pancreatectomy, neoplasia..etc
- 5)endocrinopathies.. Acromegaly, Cushing syndrome, pheochromocytoma
- 6)infections.. CMV, coxsackievirus B , congenital rubella.
- 7)drugs.. steroids

## TYPE 1 Diabetes :-

- It accounts for **10%** of all cases .
- Is an **autoimmune** disease destructing Pancreatic B cells leading to an absolute deficiency of insulin
- Most commonly develops in **childhood**, becomes manifest at puberty, and patients **depend on exogenous insulin for survival**; without insulin they develop complications
- The classic manifestations of the disease occur late in its course, after **90%** of the beta cells have been destroyed.
- genetic predisposition.

## Pathogenesis:- autoimmune:

- a. Defective deletion of self-reactive T cells in the thymus,
- b. defects in the functions of regulatory T cells
- c. Autoantibodies against B cell antigens, including insulin and enzyme glutamic acid decarboxylase, are detected in the blood of 70% to 80% of patients

???

Effects of viral infections.

## **Type 2 diabetes :**

Accounts for 80% to 90% of cases

- Caused by a combination of
  - a. Peripheral resistance to insulin action and
  - b. An inadequate compensatory response of insulin

## Insulin resistance: :

- Is defined as the failure of target tissues to respond normally to insulin
- It leads to decreased uptake of glucose in muscle, reduced glycolysis in the liver.

**Obesity and Insulin Resistance** :Visceral obesity is common in majority of affected patients and insulin resistance is present even with simple obesity unaccompanied by hyperglycemia, indicating a fundamental abnormality of insulin signaling in states of fatty excess.

The risk of diabetes increases as the body mass index increases, suggesting a dose-response relationship between body fat and insulin resistance.

Obesity and insulin resistance:

A. Role of excess free fatty acids (FFAs): The level of intracellular triglycerides often is markedly increased in muscle and liver tissues in obese persons because excess circulating FFAs are deposited in these organs

- Intracellular triglycerides are potent **inhibitors of insulin signaling and result in an acquired insulin resistance**

b. Role of inflammation: mediated by **cytokines** secreted in response to excess FFAs results in peripheral insulin resistance and beta cell dysfunction

- Excess FFAs within macrophages and beta cells can engage the *inflammasome*, leading to secretion of the IL-1 $\beta$  which mediates secretion of additional cytokines from macrophages, that are released into the circulation and act on the major sites of insulin action to promote insulin resistance

c. Role of adipokines: Adipose tissue release **adipokines** e.g IL-1 $\beta$  which promote peripheral insulin resistance

# Beta cell dysfunction

- Inability of beta cells to meet the increased demand on insulin due to peripheral resistance.
- Cause: multifactorial and overlap with those related to peripheral resistance.
- Examples: -FFAs cause cytokine release from the pancreatic Islets causing inflammatory damage.
  - Amylin, is secreted by the  $\beta$ - cells and its abnormal aggregation results in amyloid that replaces the islets.

## MORPHOLOGY of DM : Pancreas

- a. Reduction in the number and size of islets, most often in type 1 particularly with rapidly advancing disease.
- b. Leukocytic infiltration of the islets: seen in both type 1 and type 2 DM although it is more severe in type 1
  - In both types inflammation is often absent by the time the disease is clinically evident
- c. Amyloid replacement of islets in long-standing type 2 diabetes, appear as deposition of pink, amorphous material beginning in capillaries between cells
- d. At advanced stages the islets may undergo fibrosis.

# Clinical features of DM

(Frequent Urination)



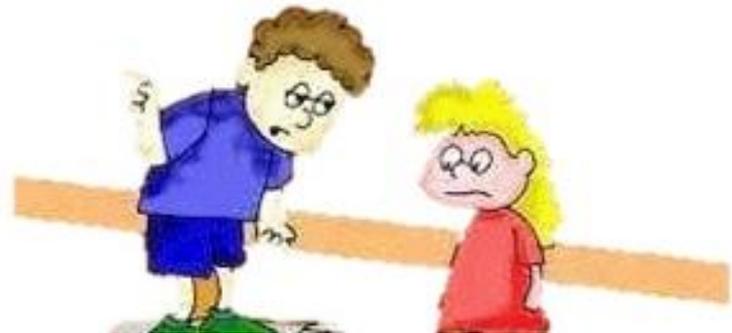
(Excessive Thirst)



Polyphagia (Excessive Hunger/Increased Appetite)



Involuntary Weight Loss



## clinical features

- a. The hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria induces an osmotic diuresis and *polyuria*,
- b. The obligatory renal water loss combined with the hyperosmolarity tends to deplete intracellular water, triggering the thirst centers of the brain and this generates intense thirst (*polydipsia*).
- c. Deficiency of insulin leads to catabolism of proteins and fats which tends to induce a negative energy balance, which in turn leads to increasing appetite (*polyphagia*)

# COMPLICATIONS OF DM

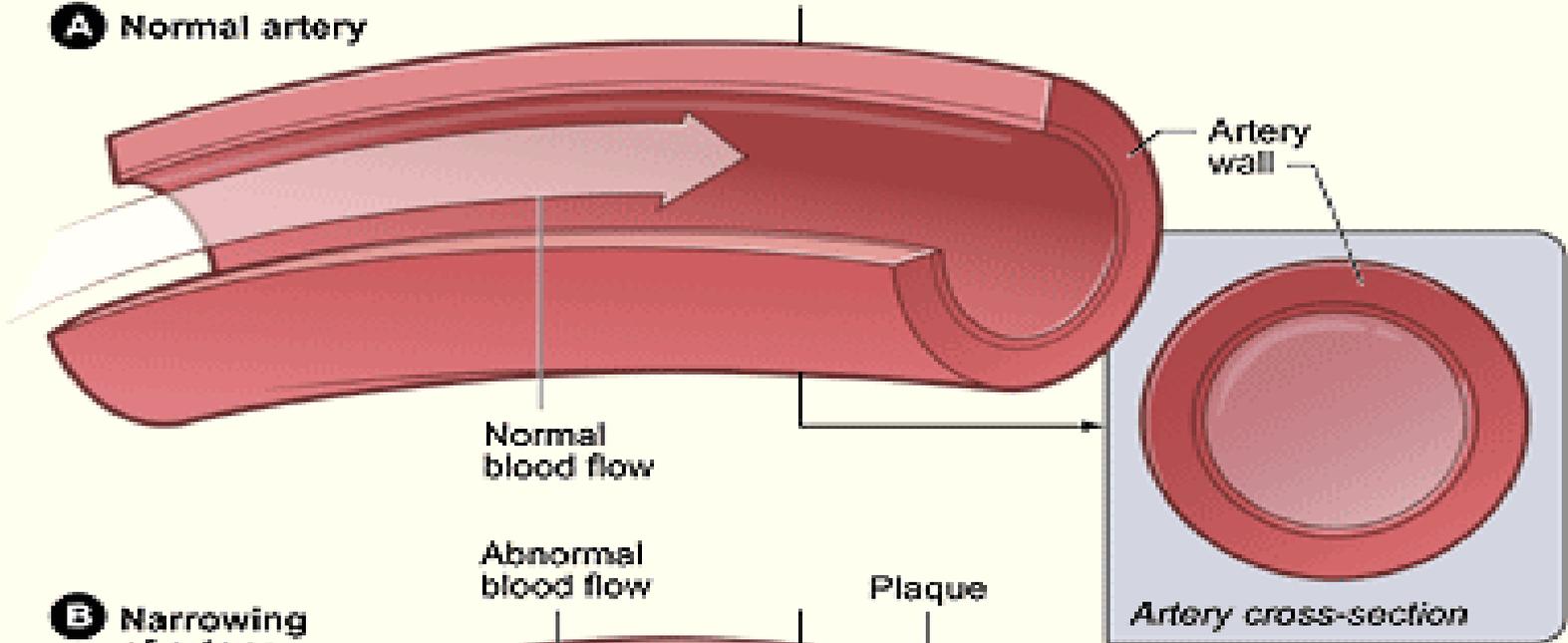
- Blood vessels: atherosclerosis, hyaline arteriosclerosis, microangiopathy
- Nephropathy : Glomerular lesions, arteriosclerosis, pyelonephritis.
- Ocular complications
- neuropathy

# Morphology and clinical manifestations of complications

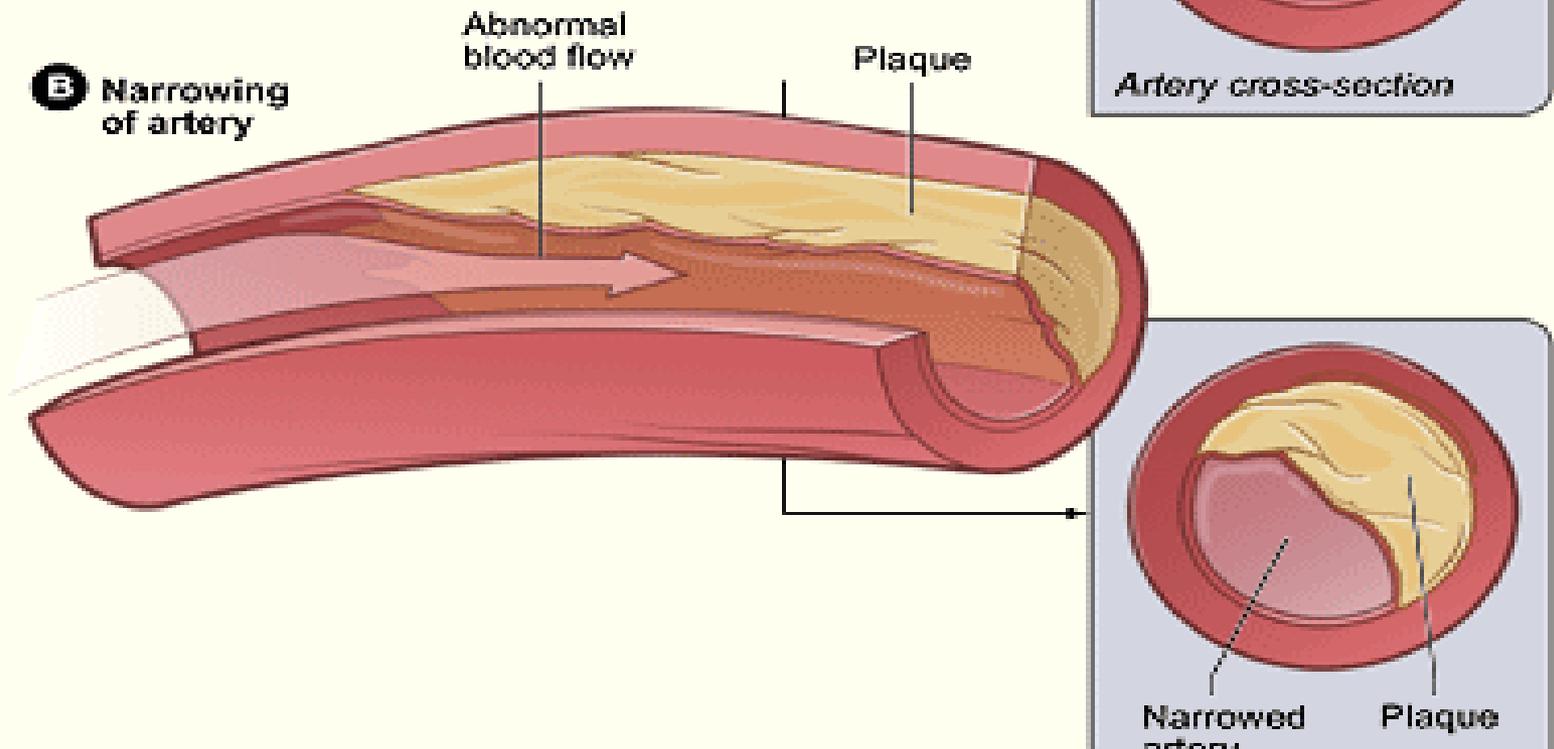
## 1. Diabetic Macrovascular Disease.:

- The hallmark is accelerated atherosclerosis affecting the aorta , large and medium-sized arteries and it is more severe with early onset in diabetics than in nondiabetics
- **Myocardial infarction** due to Coronary artery atherosclerosis is the **most common cause of death in diabetics** and is as common in diabetic women as in diabetic men
- **Gangrene** of the lower extremities is 100 times more common in diabetics than in the general population ..

**A** Normal artery



**B** Narrowing of artery



## 2. Hyaline arteriolosclerosis,

- Is the vascular lesion associated with hypertension
- Is both more prevalent and more severe in diabetics than in nondiabetics, but it is not specific for diabetes and may be seen in elderly persons who do not suffer from either diabetes or hypertension.
- It takes the form of hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen
- In diabetic patients, its severity is related not only to the duration of the disease but also to the presence or absence of hypertension.

# Hyaline arteriosclerosis

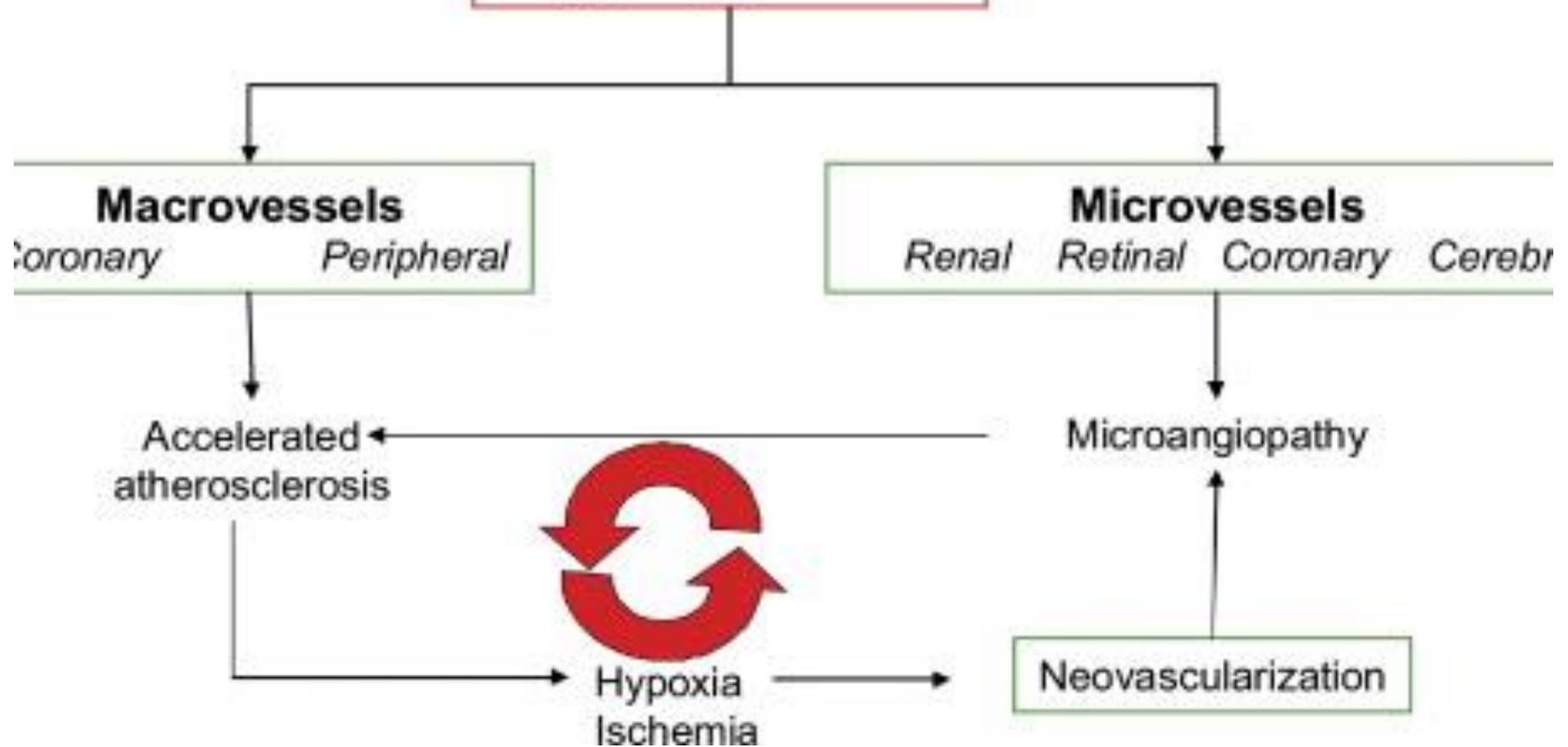


### **3. Diabetic Microangiopathy. :**

Diffuse thickening of basement membranes, is most evident in the capillaries of the skin, skeletal muscle, retina and , renal glomeruli,

- It may be seen in renal tubules, nerves, and placenta.
- It underlies the development of diabetic nephropathy, retinopathy , and some forms of neuropathy

# Hyperglycemia



## **4. Diabetic Nephropathy.:**

- The kidneys are prime targets of diabetes and renal failure is second only to myocardial infarction as a cause of death from this disease

lesions encountered are:

- Glomerular lesions, several forms of glomerulonephritis occur.**
- Renal atherosclerosis and arteriolosclerosis .**
- Pyelonephritis**,: inflammation in the interstitial tissue and involve the tubules and it has both acute and chronic forms

## **5. Ocular Complications of Diabetes:**

- Visual impairment, and blindness, is one of the more feared consequences of long-standing DM.
- Retinopathy, the most common pattern, consists of changes that are considered by many ophthalmologists to be virtually diagnostic of the disease

### Note:

- DM currently is the fourth leading cause of acquired blindness in the United States.
- About 60% to 80% of patients develop a form of diabetic retinopathy approximately 15 to 20 years after diagnosis
- diabetic patients also have an increased propensity for glaucoma and cataract formation

## 6. Diabetic Neuropathy:

- a. The most frequent pattern of involvement is that of a **peripheral, symmetric neuropathy of the lower extremities affecting motor and sensory nerves**
- b. Autonomic neuropathy produces disturbances in bowel and bladder function and sometimes sexual impotence,
- C . Mononeuropathy, which may manifest as sudden foot drop or wrist-drop or isolated cranial nerve palsies
- The neurologic changes may be the result of **microangiopathy** and increased permeability of capillaries that supply the nerves, as well as **direct axonal damage**

*Thank  
you*

