Diabetes Mellitus lecture six

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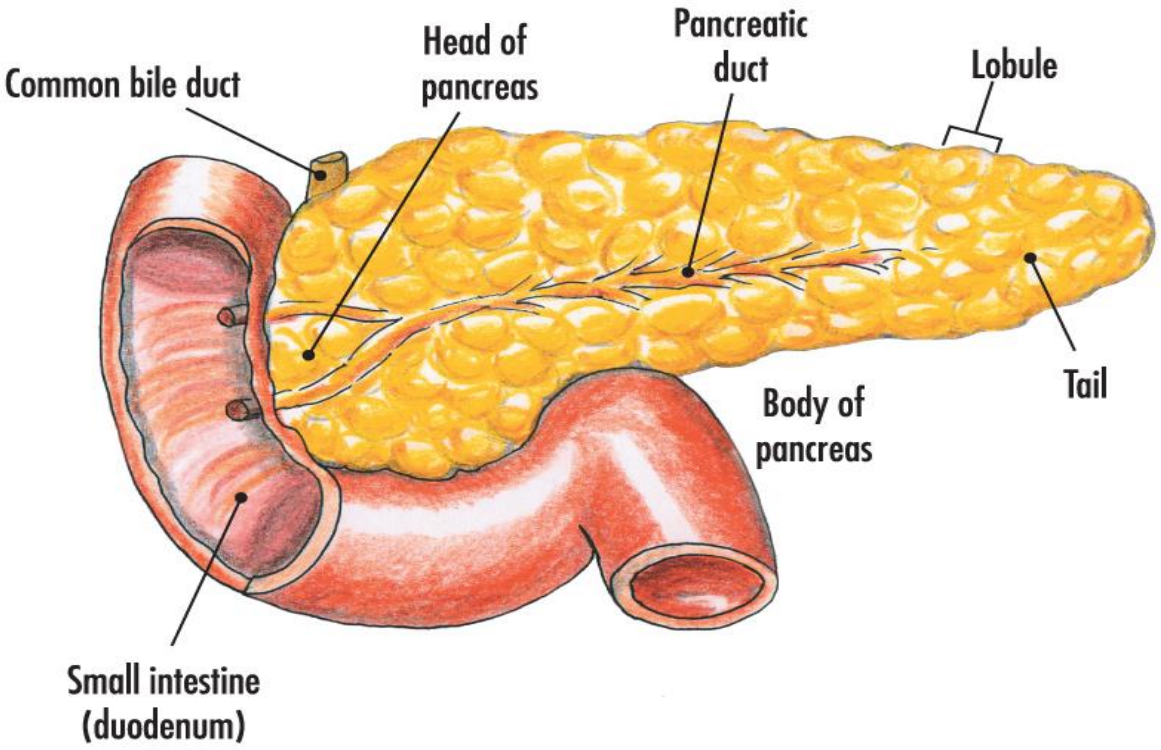
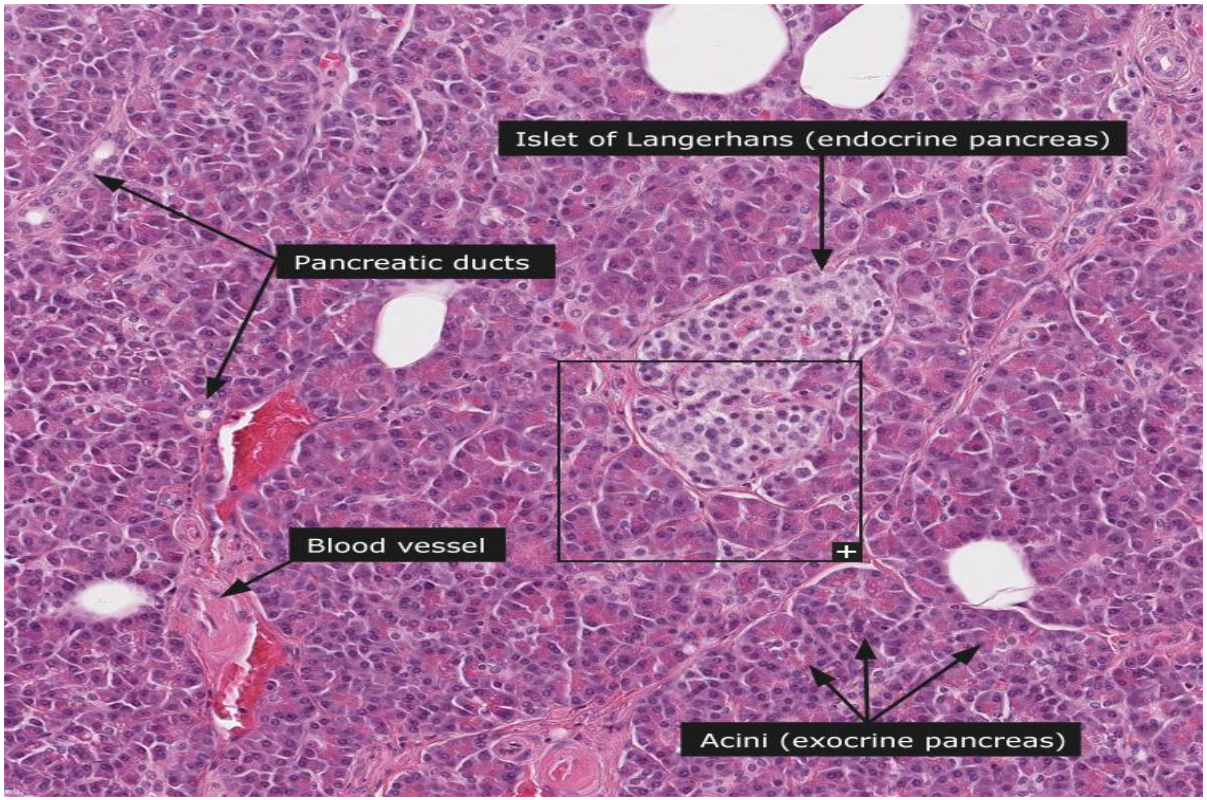
The pancreas

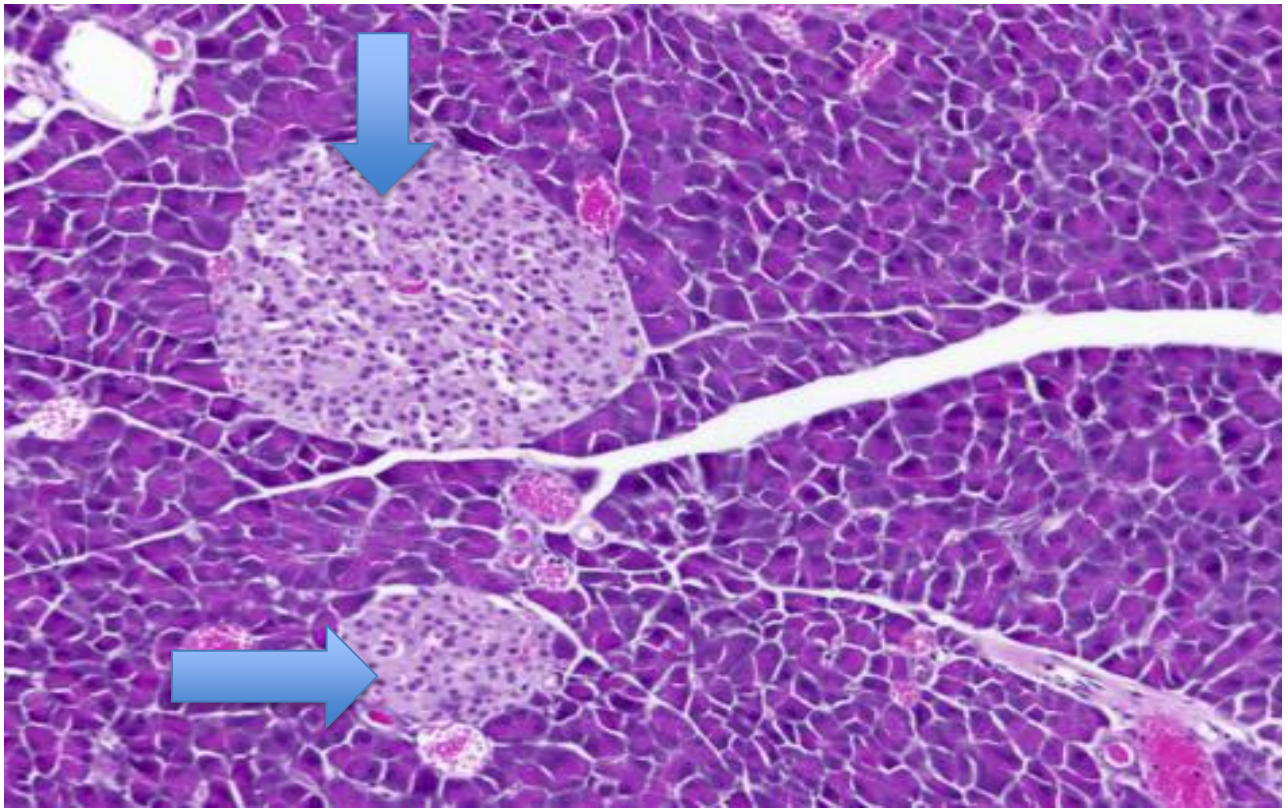


Exocrine pancreas= glands and ducts that secrete enzymes, mainly for digestion.

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 effects

- 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.

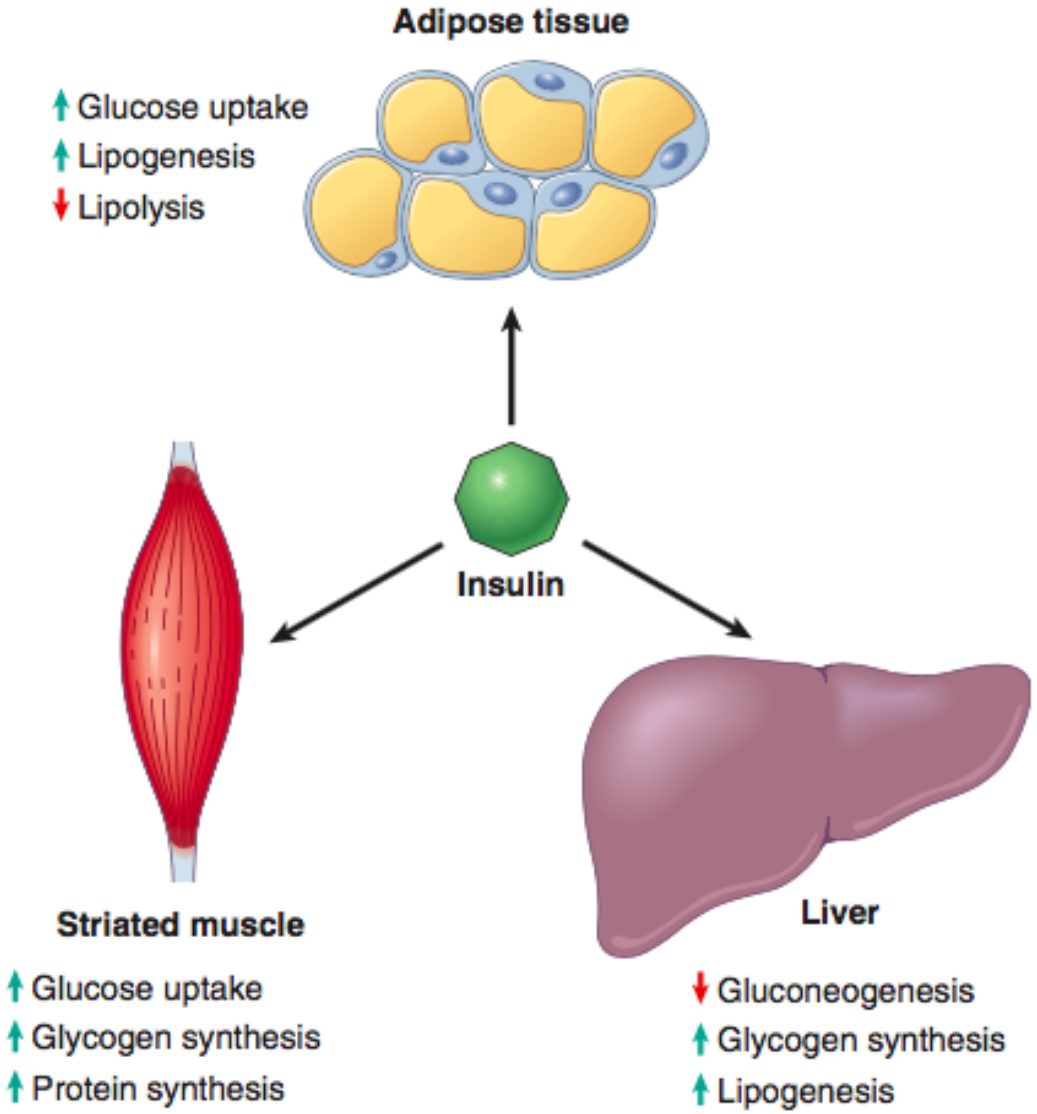


Fig. 20.21 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

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.

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 disease
- The main immune abnormality is failure of self tolerance in T-cells specific for beta cells antigens and this failure results from combination of

A .Defective clonal deletion of self reactive T-cells in the thymus and

b. Abnormalities of regulatory T-lymphocytes that normally dampen effector-T-cell responses

-

- Therefore this will lead to production of 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 of Diabetes mellitus

- Caused by a combination of

a. Peripheral resistance to insulin action and

b. B- cell dysfunction

- B-cell dysfunction is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia

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.

- The liver, skeletal muscles and adipose tissue are the major tissues where insulin resistance manifests as follows

a. failure to inhibit gluconeogenesis in the liver which contributes to high fasting blood glucose levels
b. Abnormally low glucose uptake and glycogen synthesis in the skeletal muscle

following a meal , which contributes to high postprandial blood glucose level

c. Failure to inhibit hormone-sensitive lipase in adipose tissue leading to excess circulating free fatty acids

Obesity and Insulin Resistance :

- Visceral obesity is common in majority of affected patients with type 2 DM
- and insulin resistance is present even with simple obesity un-accompanied 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.

- Metabolic syndrome is characterized by constellation of finding including

a. Visceral obesity
b. Insulin resistance
c. Glucose intolerance
d. Cardiovascular risk factors such as hypertension and abnormal lipid profile

- In diabetes it is not only the absolute amount but the distribution of body fat that has an effect on insulin sensitivity
- Central obesity (abdominal fat) is more likely to be associated with insulin resistance than in peripheral fat (gluteal/subcutaneous) obesity

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-1β 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 is not just a passive storage tissue for fat
- It is also an endocrine organ that releases hormones in response to changes in the metabolic status
- A variety of proteins secreted into the systemic circulation by adipose tissue

- and these molecules are called adipokines or adipose cytokines and some of them cause hyperglycemia and others such as leptin and adiponectin that decrease blood glucose by increasing insulin sensitivity in peripheral tissue

- Adiponectin is decreased in obesity therefore leading to 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 β- 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 .

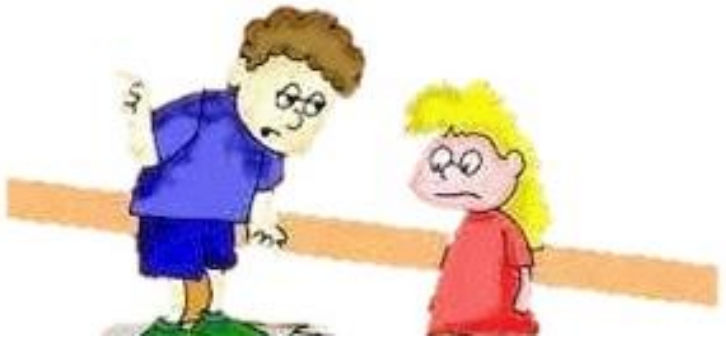
Clinical features of DM

(Frequent Urination)

(Excessive Thirst)

Polyphagia (Excessive Hunger/Increased Appetite)

Involuntary Weight Loss



clinical features

a. The hyperglycemia exceeds the renal threshold forwater 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)*

Acute complications of Diabetes mellitus

- In patients with type 1 diabetes , unusual physical activity, infection or any other form of stress worsen the metabolic imbalance leading to **diabetic ketoacidosis**

Pathogenesis

- The plasma glucose is in the range of 500 to 700 mg/dl because of absolute deficiency of insulin and unopposed effects of counterregulatory hormones (epinephrine and glucagon)

- The marked hyperglycemia causes osmotic diuresis and dehydration

Activation of ketogenic machinery

- Insulin deficiency leads to activation of hormone-sensitive lipase with resultant excessive break down of adipose tissue giving rise to increase of Free fatty acids which are oxidized in the liver to produce ketones

- Ketogenesis is an adaptive phenomenon in times of starvation generating ketones as a source of energy for consumption by vital organs (brain)
- The rate of which ketones are formed may exceed the rate at which ketones they can be used by peripheral tissues leading to ketonemia and ketonuria

- If the urinary excretion of ketones is compromised by dehydration, the accumulating ketones decrease blood PH resulting in metabolic acidosis

Long term complications of DM

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

Morphology and clinical manifesations of complications

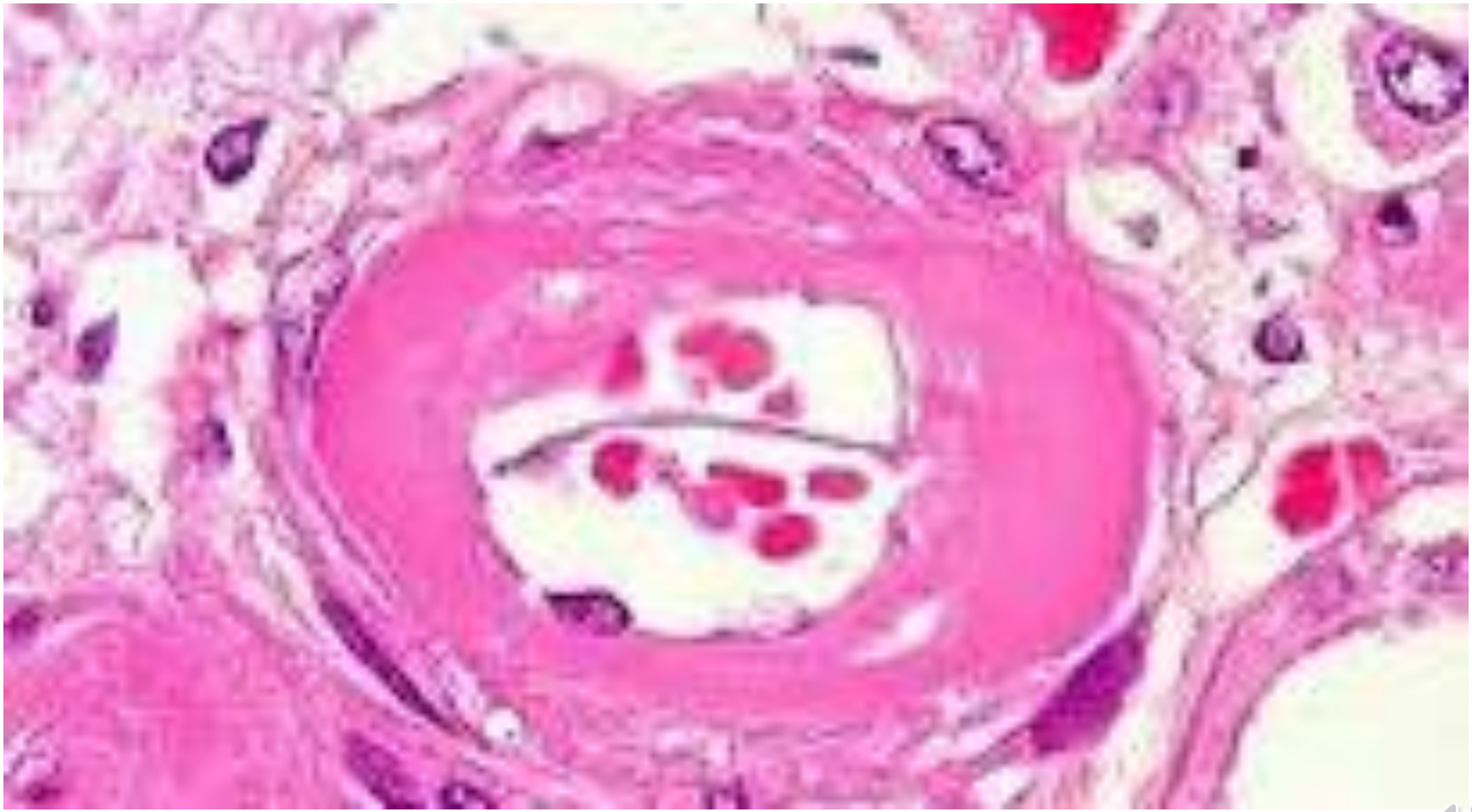
1. Diabetic Macrovascular Disease.:

- 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 athero-sclerosis 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 ..

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 arteriolosclerosis



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

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:

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

Clinical manifestations of diabetic nephropathy

- Is a leading cause of end stage renal disease in the united states
- The earliest manifestation of diabetic nephropathy is the appearance of small amounts albumin in the urine (more than 30 and less than 300 mg/day) called microalbuminuria
- Without specific interventions, approximately 80% of patients with type 1 DM and 20-40% of patients with type 2 DM will develop overt nephropathy

with macroalbuminuria excretion of more than 300 mg/day over 10 to 20 years, usually accompanied by hypertension

- By 20 years after diagnosis more than 75% of patients with type 1 diabetes and 20% of patients with type 2 DM with overt nephropathy will develop end stage renal disease necessiating dialysis or renal transplantation

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

- 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 bilateral peripheral, symmetric neuropathy of the lower extremities affecting motor and sensory nerves mainly sensory

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

Glycemic control

- Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin known as HbA1C which is formed by nonenzymatic addition of glucose to hemoglobin in red blood cells
- Unlike blood glucose levels, HbA1C is a measure of glycemic control over long period of time(2-3 months) unaffected by day to day variation
- The recommendation is to maintain HbA1C at less than 7% to reduce the risk for long term complications