PATHOLOGY TEAM

Leaders

Hazim Jokhadar & Sadeem Al-dawas

Done By

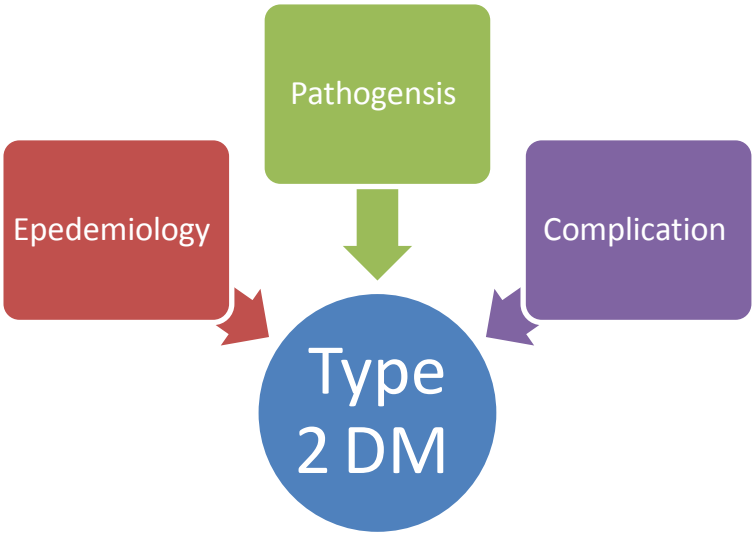
Turki Al-turki & Rawan Al-hayyan

Revised By

Majed Al-shemari

RED: Important infos. | Orange box: for the extra infos. in the comments of lecturer slids and talks | Blue box: for the infos. quoted from Robbins.

Type 2 DM



Type 2 DM, Epidemiology:

Almost 10%of persons older than 65 years of age are affected, and 80% of patients with T2DM are overweight (obese adult and elderly)

Heterogeneous disorder characterized by a combination of reduced tissue sensitivity to insulin and inadequate secretion of insulin from the pancreas.

reduced tissue sensitivity to insulin is the most important pathogenic factor.

The disease usually develops in adults, with an increased prevalence in obese persons and in the elderly.

Why aging increase the incidence of type 2 DM?

Because the aging of the cell (increase oxidative enzymatic reaction) .(it is not mention by the doctor)

Why obesity increase the incidence of type 2 DM?

Recently, T2DM has been appearing in increasing numbers in younger adults and adolescents, owing to worsening obesity and lack of exercise in this age group.

Hyperglycemia in T2DM is a failure of the B-cells to meet an increased demand for insulin in the body.

What is worse coma because hyperglycemia or hypoglycemia?

Hypoglycemia – it is much more serious because the harmful effect on the brain

T2 DM, PATHOGENESIS:

Complex interplay between underlying resistance to the action of insulin in its metabolic target tissues and reduction in glucose-stimulated insulin secretion.

Progression to overt diabetes in susceptible populations occurs most commonly in patients exhibiting both of these defects

1- GENETIC FACTORS:

Multi-factorial

Sixty percent of patients have either a parent or a sibling with the disease.

Among monozygotic twins, both are almost always affected.

No association with genes of the major histocompatibility complex (MHC), as seen in T1DM

The inheritance pattern is complex and thought to be due to multiple interacting susceptibility genes.

Constitutional factors such as obesity (which itself has strong genetic determinants), hypertension, and the amount of exercise influence the phenotypic expression of the disorder

2- GLUCOSE METABOLISM:

In a normal person, the extracellular concentration of glucose in fed and fasting states is maintained in a tightly limited range.

This rigid control is mediated by the opposing actions of insulin and glucagon.

Following a carbohydrate-rich meal, absorption of glucose from the gut leads to an increase in blood glucose, which stimulates insulin secretion by the pancreatic B-cells and the consequent insulin-mediated increase in glucose uptake by skeletal muscle and adipose tissue.

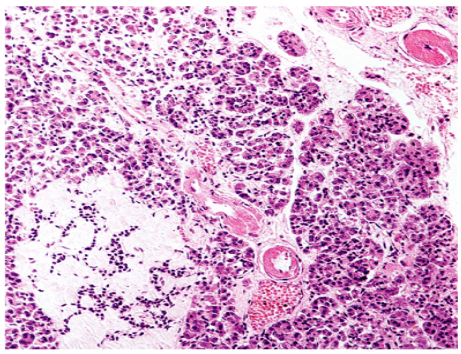
At the same time, insulin suppresses hepatic glucose production (prevent the glucose sending from the liver to the periphery)

3- B-CELL FUNCTION

Persons with T2DM exhibit impaired B-cell insulin release in response to glucose stimulation

This functional abnormality is specific for glucose, since the B-cells retain the ability to respond to other stimulants, such as amino acids.

B-cell function may also be affected by the chronically elevated plasma levels of free fatty acids that occur in obese persons.



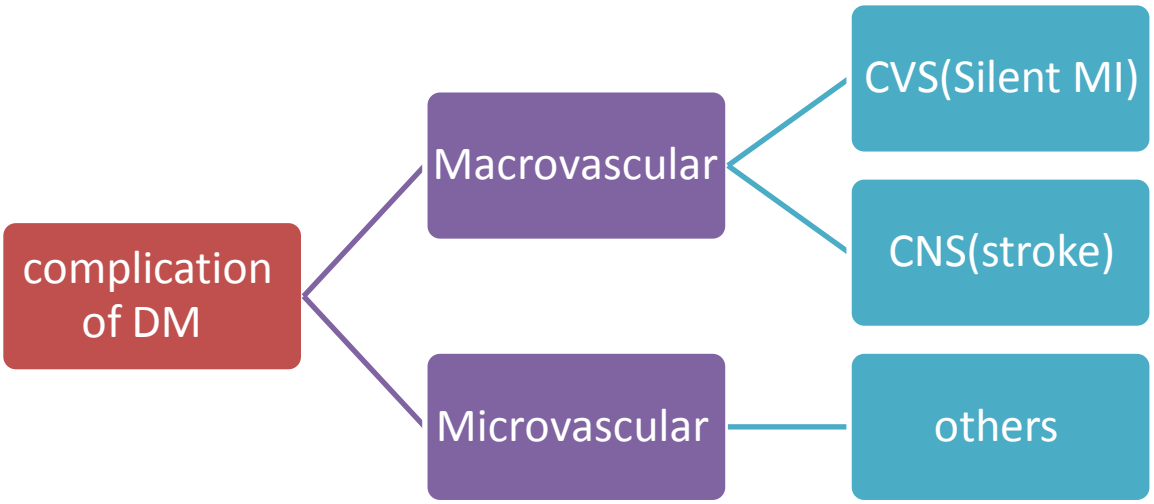
No consistent reduction in the number of B-cells

No morphologic lesions of B- cells

In some islets, fibrous tissue accumulates, sometimes to such a degree that they are obliterated.

Islet amyloid is often present particularly in patients over 60 years of age

On histopathology we may not know if the person have Type2 DM because there is no specific findings



Diabetic Microvascular Disease:

The most common complication

Responsible for Many of the Complications of Diabetes, Including Renal Failure and Blindness (diabetic nephropathy it is always related to diabetic retinopathy)

Arteriolosclerosis and capillary basement membrane thickening are characteristic vascular changes in diabetes.

The frequent occurrence of hypertension contributes to the development of the arteriolar lesions. In addition, deposition of basement membrane proteins, which may also become glycosylated, increases in diabetes.

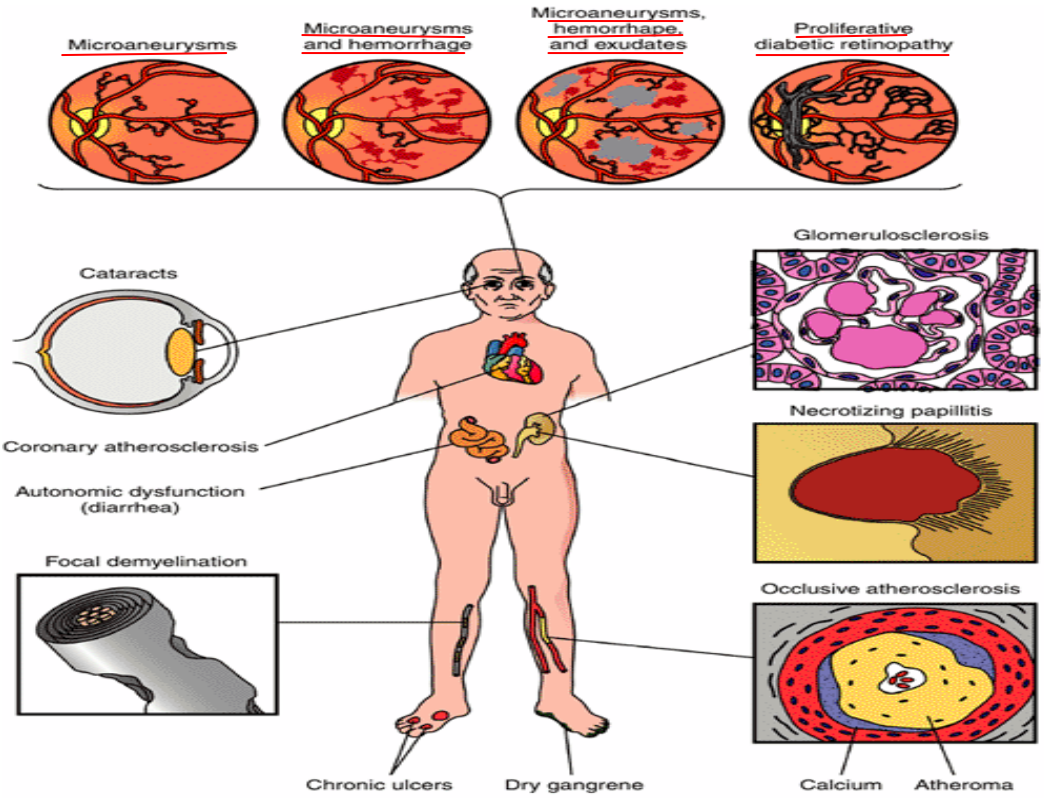
Aggregations of platelets in smaller blood vessels and impaired fibrinolytic mechanisms have also been suggested as playing a role in the pathogenesis of diabetic microvascular disease.

If there is a hyalinization of arteries we can't differentiate if is it HTN or DM however if there is a hyalinization of afferent and efferent arterioles in kidney more likely DM

The effects of microvascular disease on tissue perfusion and wound healing are profound

Reduce blood flow to the heart, which is already compromised by coronary atherosclerosis.

Healing of chronic ulcers that develop from trauma and infection of the feet in diabetic patients is commonly defective



Diabetic Nephropathy:

30% to 40% of T1DM ultimately develop renal failure. A somewhat smaller proportion (up to 20%) of patients with T2DM are similarly affected

Diabetic nephropathy accounts for one third of all new cases of renal failure.

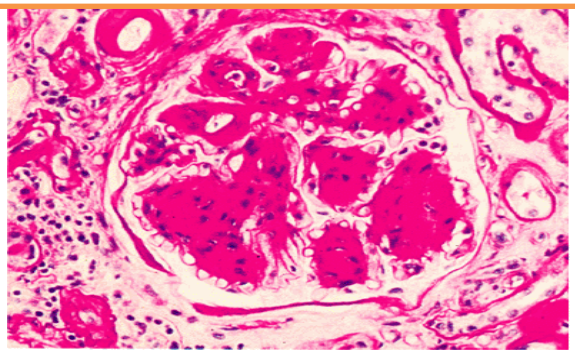
The prevalence of diabetic nephropathy increases with the severity and duration of the hyperglycemia.

Kidney disease due to diabetes is the most common reason for renal transplantation in adults.

The glomeruli in the diabetic kidney exhibit a unique lesion termed *Kimmelstiel-Wilson* disease or nodular glomerulosclerosis

What is the pathogenic mechanism behind nodular glomerulosclerosis ?

Microanurysm will be filled with menstric matrix and form nodule.



Diabetic Retinopathy: (most frequent complication Dr.Hala)

The most devastating ophthalmic complication of diabetes

The most important cause of blindness in the Unites States in persons under the age of 60 years.

The risk is higher in T1DM than in T2DM.

10% of patients with T1DM of 30 years' duration become legally blind. There are many more patients with T2DM, so these are the most numerous patients with diabetic retinopathy.

Diabetic Neuropathy:

Characterized by pain and abnormal sensations in the extremities.

The most common and distressing complications of diabetes.

Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.

Affects Sensory and Autonomic Innervations, Peripheral sensory impairment, and autonomic nerve dysfunction.

Changes in the nerves are complex, and abnormalities in axons, the myelin sheath, and Schwann cells have all been found.

Peripheral neuropathy can leads to foot ulcers.

Plays a role in the painless destructive joint disease that occasionally occur.

Not only from insufficient blood supply – it is also from the cell itself such us the shwan cell = myelin sheath destruction

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.

Gestational diabetes:

Diabetes Occurring During Pregnancy

May put both Mother and Fetus at risk

Develops in only a few percent of seemingly healthy women during pregnancy.

It may continue after parturition in a small proportion of these patients.

Pregnancy is a state of insulin resistance.

These women highly susceptible to overt T2DM later in life.

yremmuS:

Type 2 diabetes has no autoimmune basis; instead, features central to its pathogenesis are insulin resistance and β-cell dysfunction, resulting in relative insulin deficiency.Obesity has an important relationship with insulin resistance (and hence, type 2 diabetes)

oitseuQsen:

Patient known to have diabetes for 30 years recently he died after end stage renal disease, if we examine the pancreas we will see:

1-Amyloid deposition.

2-Neutrophils.

3-Granuloma.

Patient come to the clinic with black eschar in the nose what could be the possible complication:

1-Group A streptococcus infection.

2-Mucormycosis.

3-Diabetic neuropathy.

Diabetic retinopathy commonly seen in which type of diabetes:

1-Type 1

2-Type 2

3- Gestational diabetes.

3- A 55-year-old obese woman (body mass index = 33 kg/m2) complains of declining visual acuity. Funduscopic examination shows peripheral retinal microaneurysms. Urinalysis reveals 3+ proteinuria and 3+ glucosuria. Serum albumin is 3 g/dL, and serum cholesterol is 350 mg/dL. These clinicopathologic fi ndings are best explained by which of the following mechanisms of disease?
(A) Anti-insulin antibodies
(B) Increased peripheral insulin uptake
(C) Irregular insulin secretion
(D) Peripheral insulin resistance
(E) Secretion of insulin-like proteins

4- A 61-year-old man presents with a 5-year history of pain in both legs during exercise. He has been treated for diabetes for 8 years. His fasting blood glucose is 280 mg/dL. Which of the following best explains the pathogenesis of leg pain in this patient?
(A) Atherosclerosis
(B) Malignant hypertension
(C) Microaneurysms
(D) Peripheral neuropathy
(E) Vasculitis

5- A 60-year-old man with diabetes mellitus complains of deep burning pain and sensitivity to touch over his hands and fi ngers. Nerve conduction studies show slow transmission of impulses and diminished muscle stretch refl exes in the ankles and knees. Sensations to vibrations and light touch are also markedly diminished. The development of polyneuropathy in this patient correlates best with which of the following conditions?
(A) Anti-insulin antibody titer
(B) Hyperglycemia
(C) Insulin defi ciency
(D) Intermittent hypoglycemia
(E) Ketoacidosis

6- A 56-year-old man with a 14-year history of diabetes mellitus presents with poor vision, peripheral vascular disease, and mild proteinuria. Which of the following is the best monitor of the control of blood sugar levels in this patient?

(A) Glycosylated hemoglobin
(B) Islet cell autoantibody
(C) Serum myoinositol
(D) Serum sorbitol

(E) Serum triglycerides

7- A 65-year-old obese man (body mass index = 32 kg/m2) presents with a 2-year history of diffi culty walking. Physical examination reveals chronic ulcers in the lower extremities. Funduscopic examination reveals proliferative retinopathy. Which of the following best describes the pathogenesis of chronic ulcers on the legs of this patient?

(A) Abnormal glycosylation of hemoglobin
(B) Inadequate leukocytic response to infection
(C) Low concentrations of insulin in tissues
(D) Microvascular disease
(E) Varicose veins

8- Thickening of small vessel basement membranes in the patient described in Question 7 is most likely related to abnormalities in which of the following cellular and biochemical processes?

(A) Amyloidosis
(B) Collagenous fi brosis
(C) Glycosylation
(D) Immunoglobulin deposition
(E) Insudation of fi brin

9- A 58-year-old man with a long-standing history of type 2 diabetes mellitus suffers a massive hemorrhagic stroke and expires. Examination of the pancreas shows hyalinization of many islets of Langerhans. Which of the following characterizes the material within the islets of Langerhans?

(A) Amyloid
(B) Collagen type IV
(C) Fibrin
(D) Fibronectin
(E) Proteoglycan

11- A 75-year-old woman with well-controlled diabetes complains of poor eyesight. A grayish-white opacifi cation of the lens is found during a comprehensive eye examination. Which of the following metabolic pathways is most likely involved in this lens abnormality?

(A) Aldose reductase pathway
(B) Amino acid degradation cycle
(C) Citric acid cycle
(D) Oxidative phosphorylation
(E) Pentose-phosphate shunt

12- A 40-year-old diabetic woman complains of fl ank pain and fever. Her temperature is 38.7°C (103°F), respirations are 25 per minute, and blood pressure is 150/90 mm Hg. Urinalysis reveals pyuria with WBC casts. Which of the following features of diabetes is the most important contributing factor in the development of fl ank pain and fever in this patient?

(A) Anti-insulin antibodies
(B) Glycosylation of hemoglobin
(C) Hyperglycemia
(D) Peripheral insulin resistance
(E) Sorbitol accumulation

13- A 32-year-old woman with diabetes mellitus delivers a child after 38 weeks of gestation. Which of the following is the most likely abnormality that might be encountered in this child at birth?

(A) Cataracts
(B) Hyperbilirubinemia
(C) Hypoglycemia
(D) Low birth weight
(E) Mental retardation

14- An obese woman (body mass index [BMI] = 32 kg/m2) presents for a routine physical examination. In reviewing your patient's health status, you mention that obesity is associated with an increased incidence of which of the following diseases?

(A) Cardiomyopathy
(B) Cervical carcinoma
(C) Chronic obstructive pulmonary disease
(D) Degenerative joint disease
(E) Diabetes mellitus type 1

Answeres:

1,2,1

3- The answer is D: Peripheral insulin resistance. Type 2 diabetes mellitus results from a complex interplay between underlying resistance to the action of insulin in its metabolic target tissues (liver, skeletal muscle, and adipose tissue) and a reduction in glucose-stimulated insulin secretion, which fails to compensate for the increased demand for insulin. In obese persons, the release of inhibitory mediators from adipose tissue interferes with intracellular signaling by insulin. Hyperinsulinemia secondary to insulin resistance also downregulates the number of insulin receptors on the plasma membrane. The other choices have not been related to the pathogenesis of type 2 diabetes.
Diagnosis: Diabetes mellitus, type 2
4- The answer is A: Atherosclerosis. The extent and severity of atherosclerotic lesions in medium-sized and large arteries are increased in patients with long-standing diabetes. Leg pain during walking or exercise, which forces the patient to stop or limp (intermittent claudication) is typically a complication of atherosclerosis involving the major arteries of the lower extremities. Peripheral neuropathy (choice D) is a complication of diabetes but is an unlikely cause of claudication. Diabetes does not cause vasculitis (choice E).
Diagnosis: Atherosclerosis
5- The answer is B: Hyperglycemia. The severity and chronicity of hyperglycemia in both T1DM and T2DM are the major pathogenetic factors leading to the microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy. Thus, control of blood glucose remains the major

means by which the development of microvascular diabetic complications can be minimized. Glucose binds nonenzymatically by attaching to a variety of proteins. This process, termed glycosylation, occurs roughly in proportion to the severity of hyperglycemia. Unfortunately, trials in which blood glucose levels were carefully controlled did not necessarily prevent all complications of diabetes.
Diagnosis: Diabetic neuropathy
6- The answer is A: Glycosylated hemoglobin. A specifi c fraction of glycosylated hemoglobin in circulating red blood cells (hemoglobin A1c) is measured routinely to monitor the overall degree of hyperglycemia that occurred during the preceding 6 to 8 weeks. Nonenzymatic glycosylation of hemoglobin is irreversible, and the level of hemoglobin A1c, therefore, serves as a marker for glycemic control. None of the other choices are quantitative measures of glucose levels.
Diagnosis: Diabetes mellitus
7- The answer is D: Microvascular disease. Microvascular disease, a characteristic complication of diabetes, causes ischemia and is, in part, responsible for the slow healing of wounds in the diabetic patient. It also results in other complications of diabetes such as renal disease. In addition to microvascular disease, aggregation of platelets in the smaller blood vessels and impaired fi brinolytic mechanisms have also been suggested to play a role in the pathogenesis of diabetic microvascular disease. The susceptibility of diabetics to infection is a complex problem, but it does not seem that the functions of polymorphonuclear leukocytes are directly affected (choice B). The tissue concentration of insulin (choice C) does not infl uence the healing process. Diabetes mellitus does not predispose to varicose veins (choice E).
Diagnosis: Diabetic microvascular disease
8- The answer is C: Glycosylation. Increased deposition and glycosylation of basement membrane proteins contribute to the pathogenesis of diabetic microvascular disease. Thus, control of blood glucose remains the major means by which the development of microvascular diabetic complications can be minimized.

The other choices do not preferentially accumulate in small vessels affected by diabetes.
Diagnosis: Diabetic microvascular disease
9- The answer is A: Amyloid. In T2DM, amyloid is often present within the islets of Langerhans, particularly in patients over 60 years of age. This type of amyloid derives from a polypeptide molecule known as amylin, which is secreted with insulin by the ®-cell. As many as 20% of aged nondiabetic persons also have amyloid deposits in the pancreas, which is a fi nding that has been attributed to the aging process itself. None of the other choices show Congo red staining and apple-green birefringence under polarized light.
Diagnosis: Amyloidosis
11- The answer is A: Aldose reductase pathway. The aldose reductase pathway has been implicated in the pathogenesis of diabetic complications in some tissues, including the formation of cataracts. Glucose is converted to sorbitol (sugar alcohol), which can be cytotoxic. It is suspected to play a role in diabetic complications in a variety of tissues, including peripheral nerves, retina, lens and kidney. None of the other choices have been implicated in the pathogenesis of cataracts.
Diagnosis: Cataract
12- The answer is C: Hyperglycemia. Flank pain, fever, and pyuria are indicative of acute pyelonephritis, a common complication of diabetes. Glucose in the urine provides an enriched culture medium. In addition, patients with autonomic neuropathy often have a dystonic bladder that retains urine. Pyelonephritis

is a constant threat for patients with diabetes, and necrotizing papillitis may be a devastating complication of renal infection. The other choices are not related to renal infection.
Diagnosis: Pyelonephritis, papillary necrosis
13- The answer is C: Hypoglycemia. Tight glucose control in the diabetic mother is necessary to prevent overstimulation of the fetal pancreas during gestation. Fetuses exposed to hyperglycemia in utero may develop hyperplasia of the pancreatic ®-cells, which may secrete insulin autonomously and cause hypoglycemia at birth and in the early neonatal period. Infants of diabetic mothers show a 5% to 10% incidence of major development abnormalities. Increased birth weight is commonly encountered in offspring of diabetic mothers (see choice D). The incidence of mental retardation (choice E) is not specifi cally increased.
Diagnosis: Gestational diabetes
14- The answer is D: Degenerative joint disease. Degenerative joint disease (osteoarthritis) of weight-bearing joints is a common complication of obesity. The hips and knees are most commonly affected. Obesity is determined according to BMI, which is calculated as weight (kg)/height (m_2). A BMI of 25 to 30 kg/m_2 is classed as overweight. Obesity is a risk factor for the development of adult-onset (type 2) diabetes mellitus, but not for juvenile-onset (type 1) diabetes mellitus (choice E). Obesity by itself does not cause cardiomyopathy (choice A).
Diagnosis: Obesity