

Diabetes mellitus

Objectives

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



Black: original content
Red: Important
Blue: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides



Editing File

Diabetes mellitus



Introduction

- Group of metabolic disorders characterized by **hyperglycemia**.
- **Hyperglycemia** due to: defect in insulin secretion, action, or most commonly, both.
- It is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations in USA.

Prediabetes

- **Impaired glucose tolerance.**
- Elevated blood sugar that does not reach the criteria for diagnosis of diabetes.
- ¼ of individuals with prediabetes and additional risk factors such as obesity and family history will develop overt diabetes in the next 5 years.
- They have elevated risk of cardiovascular disease.

Manifestations

- **Triad of diabetes: Polyuria, polydipsia and polyphagia.**
- In severe cases, ketoacidosis, all resulting from metabolic derangements.
- The combination of polyphagia and weight loss.

Diagnosis

- Normal blood glucose level = 70 to 120 mg/dl.
- Diagnostic criteria for diabetes:

Test	Prediabetes	Diabetes
Fasting plasma glucose	100 - 125 mg/dL	≥ 126 mg/dl
Random plasma glucose with classic hyperglycemic signs	-	≥ 200 mg/dl
2-hour plasma glucose during an oral glucose tolerance test with a loading dose of 75 gm Mainly used to diagnose diabetes in pregnancy	140 - 199 mg/dL	≥ 200 mg/dl
Glycated hemoglobin (HbA1C) level ¹	5.7% - 6.4%	≥ 6.5%

- All tests need to be **repeated and confirmed on a separate day**, except the random glucose test.
- **The ADA recommends maintaining HbA1C below 7% to reduce risk of complications.**
- 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 requires persistence hyperglycemia and resolution of the acute illness.

1- It is used to measure glycemic control over long periods of time (2-3 months); the measure of nonenzymatic glycosylation to Hb in RBCs

Diabetes mellitus

Classification

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

Type 1 diabetes

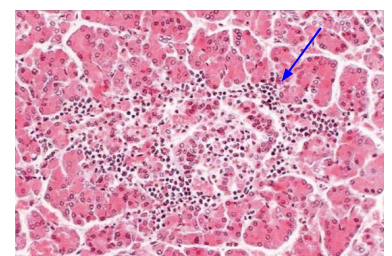
- **Autoimmune disease** characterized by gradual process of pancreatic **β -cell** destruction and an **absolute** deficiency of insulin.
- 5% to 10% of all cases.
- Most common subtype diagnosed in patients < 20 years of age.
- Although beta cell destruction is a gradual process, the transition from impaired glucose tolerance to overt diabetes may be abrupt.
- **Insulin replacement is the mainstay of treatment.**

Pathogenesis

- Islet destruction caused primarily by failure of self-tolerance in T cells specific for beta cell antigens.
- The classic manifestations of occur after >90% of the β cells have been destroyed.
- **Autoantibodies** against β cell antigens, are detected in the blood of 70% to 80% of patients.
- **Genetic susceptibility: HLA-DR3, or DR4 and Several non-HLA genes** in 90% to 95% of white patients.
- **Environmental factors:** infections.

Morphology

- Lesions in the pancreas are inconstant and rarely of diagnostic value.
 - Reduction in the number and size of islets.
 - **Insulinitis:** Leukocytic infiltration of the islets, composed of **T lymphocytes**.
- An increase in the number and size of islets, characteristic of nondiabetic newborns of diabetic mothers.



Diabetes mellitus

Diabetic Ketoacidosis

- Caused by **stress** which may worsen the metabolic imbalance.
- Plasma glucose → range from 500 to 700 mg/dL.
- **Characteristics** caused by hyperglycemia:
 - **Osmotic diuresis.**
 - **Dehydration¹.**
- **Activation of the ketogenic machinery:**
 - Insulin deficiency → excessive breakdown of adipose stores → increased FFAs → oxidized by the liver to produce ketones as a source of energy for consumption by vital organs (e.g., the brain).
 - The rate of ketones formation may exceed the rate at which they can be used by peripheral tissues, → **ketonemia** and **ketonuria**.
 - The accumulating ketones decrease blood pH, → **metabolic acidosis**.

Type 2 diabetes

- Combination of **peripheral resistance to insulin** action and **relative insulin deficiency** (inadequate secretory response by the pancreatic β cells).
- 90% to 95% of diabetic cases. Many of them are overweight.
- The prevalence in children and adolescents is increasing due to the \uparrow of obesity.
- Dietary restriction and exercise are the first line of defense: eventually they need pharmacological intervention to reduce hyperglycemia

Pathogenesis

- Heterogeneous and multifactorial complex disease that involves interactions of genetics, environmental risk factors, and inflammation.
- Characterized by **two defects**:
 - **Insulin resistance**: decreased ability of peripheral tissues to respond to insulin. The liver, skeletal muscle, and adipose tissue.
 - **Beta cell dysfunction**: that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.

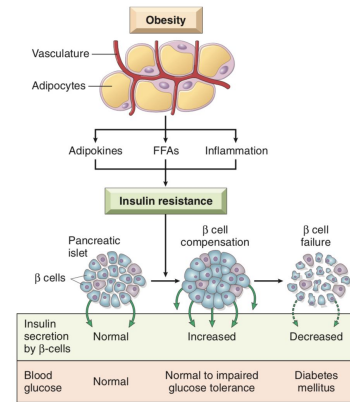
Obesity and Insulin Resistance

- **Central obesity** (abdominal fat) is more likely to be associated with insulin resistance than is peripheral (gluteal/ subcutaneous) obesity.
- **Metabolic syndrome** has been applied to several findings dominated by:
 - Visceral obesity, Insulin resistance, Glucose intolerance and Cardiovascular risk factors such as hypertension and abnormal lipid profiles.
 - High risk for the development of type 2 diabetes.

1. Rehydration is the 1st line treatment.

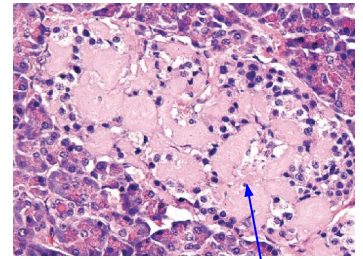
Diabetes mellitus

- Obesity can adversely impact insulin sensitivity by:
 - **Excess FFAs:**
 - Increased fasting plasma FFAs decrease insulin sensitivity.
 - **Adipokines:**
 - Normally: leptin and adiponectin decrease blood glucose, by increasing the insulin sensitivity in the peripheral tissues.
 - Obesity: Adiponectin levels are decreased 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 interleukin, and other cytokines promote insulin resistance.



Morphology

- **Amyloid** replacement of islets in long-standing type 2: deposition of pink, amorphous material.
- Fibrosis at advanced stages.



Hyperosmolar Nonketotic Coma

- Severe **dehydration** resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia.
- Seen in older adult diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.

Monogenic Forms of Diabetes

- Type 1 and type 2 diabetes are genetically complex, not single-gene mutation.
- **Monogenic forms of diabetes:** result from loss of function mutations within a **single gene**.
- **Causes:** primary defects in beta cell function and insulin receptor signaling.
- Classified based on age of onset:
 - **Neonatal period:** congenital early onset diabetes.
 - **Before 25 years of age:** maturity onset diabetes of the young (MODY).

Gestational diabetes

- Pregnancy is a “diabetogenic” state in which the hormones causes insulin resistance. In some euglycemic pregnant women this can give rise to gestational diabetes. *Could also overt to DM type 2 later in life*
- Increases the 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.

Chronic Complications of Diabetes

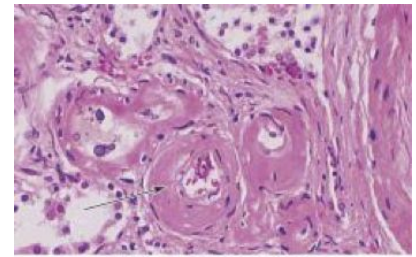


1- Macrovascular complications

- Atherosclerosis of the Aorta and large and medium-sized arteries.
- **Coronary arteries:** MI caused by atherosclerosis of the coronary arteries, is the **most common causes of death in diabetics.**
- **Large Renal Arteries:** also exhibit severe atherosclerosis, but most renal damage is in the glomeruli and microcirculation.
- Gangrene of the lower extremities, due to advanced vascular disease.

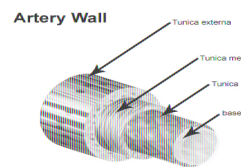
Morphology

- **Hyaline arteriosclerosis:** an amorphous, hyaline thickening of the wall of the arterioles, causing narrowing of the lumen.
- Associate with hypertension.
- It is more common and more severe in diabetics than non diabetics.



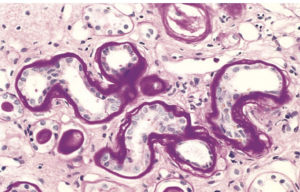
2- Microvascular complications

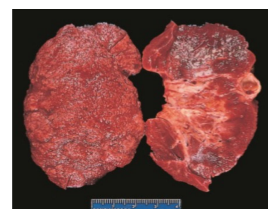
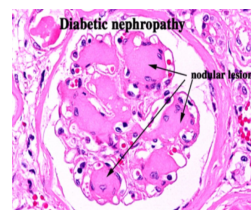
- Diffuse thickening of **basement membranes** of vessels
- Mostly seen in skin, skeletal muscles, retina, glomeruli, and renal medulla.
- Underlies the development of diabetic **nephropathy, retinopathy, and neuropathy.**
- The basal lamina is markedly thickened by concentric layers of hyaline material composed mainly of **type 4 collagen.**
- Despite increased thickness it is more leaky to plasma proteins.



3- Nephropathy

1. Glomerular lesion:

Capillary basement membrane thickening	Diffuse mesangial sclerosis	Nodular glomerulosclerosis
<p>Thickening along entire length.</p>  <p><small>Fig. 20.28 Renal cortex showing thickening of tubular basement membranes in a specimen from a diabetic patient. (Periodic acid-Schiff stain)</small></p>	<p>Diffuse increase in:</p> <ul style="list-style-type: none"> - Mesangial matrix - Mesangial cells - When glomerulosclerosis is marked: nephrotic syndrome manifests (proteinuria, hypoalbuminemia, edema). 	<p>Kimmelstiel-wilson lesion: ball-like deposits of a laminated matrix in the periphery of the glomeruli</p> <ul style="list-style-type: none"> - PAS positive - This disease is indicative of DM, found in 15-30% of patients with long term DM.



- Both diffuse and nodular glomerulosclerosis induce enough ischemia to causing scarring, indicated by finely granular-appearing cortical surface.
- Renal Failure is the second cause of death from diabetes.

Chronic Complications of Diabetes

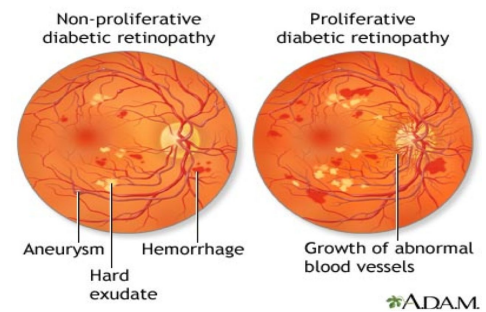
2. **Arteriosclerosis:** of the renal arteries.
3. **Pyelonephritis:** acute or chronic inflammation of the kidney.
 - Usually start with the interstitial tissue then spread to tubules.
 - More common and severe in diabetics than non diabetics.
 - **Necrotizing papillitis:** a more severe involvement, causing necrosis of the papilli; is more prevalent in diabetics.

4- Ocular Complications

- Could be retinopathy cataract formation, or glaucoma.

Morphology

- **Nonproliferative retinopathy:**
 - Hemorrhage
 - Retinal exudate (cotton wool sots) can be: Soft → microangiopathy or Hard → deposits of plasma proteins and lipids.
 - **Microaneurysm:** discrete saccular dilations or choroidal capillaries, appear as red spots on ophthalmoscopes.
 - Microangiopathy: thickening of retinal capillaries.
- **Proliferative retinopathy:** neovascularization and fibrosis
 - Leading to blindness, especially if it involves the macula.
 - And cause retinal detachment.



5- Diabetic neuropathy

- **Peripheral, symmetric neuropathy:** affecting the motor and sensory function of lower extremities. (most common form of neuropathy)
- **Autonomic neuropathy:** disturbance in bowel and bladder functions
- **Diabetic mononeuropathy:** sudden foot drop or wrist drop.
- Microvasculopathy of small vessels contribute to these disorders.

6- Infections

- Diabetics are more susceptible to infection (5% of diabetes-related death)
- Bacterial and fungal infection occur in poorly controlled hyperglycemic patients
- **Renal papillary necrosis:** could occur due to bladder infection
- **Mucormycosis:** in poorly controlled diabetes
 - Fungal infection tends originate in nasopharynx or paranasal sinus
 - Spread to orbit cavity and brain
- In patient with diabetic neuropathy: trivial infection to the toe may be the first in a long succession of complications (bacteremia, pneumonia, gangrene) that may lead to death

Summary

Type 1 Diabetes

Pathogenesis	<ul style="list-style-type: none"> • Autoantibodies against β cell antigens, are detected in the blood of 70% to 80% of Patients. • Genetic susceptibility: HLA-DR3, or DR4 and Several non-HLA genes in 90% to 95% of white patients. • Environmental factors: infections.
Morphology	<ul style="list-style-type: none"> • Reduction in the number and size of islets. • Insulinitis: Leukocytic infiltration of the islets, composed of T lymphocytes. • An increase in the number and size of islets, characteristic of nondiabetic newborns of diabetic mothers.
Diabetic Ketoacidosis	<ul style="list-style-type: none"> • Plasma glucose \rightarrow range from 500 to 700 mg/dL. • Characteristics: Osmotic diuresis and Dehydration. • Insulin deficiency \rightarrow excessive breakdown of adipose stores \rightarrow increased FFAs \rightarrow oxidized by the liver to produce ketones as a source of energy for consumption by vital organs (e.g., the brain). • The accumulating ketones decrease blood pH \rightarrow metabolic acidosis.

Type 2 Diabetes

Pathogenesis	<ul style="list-style-type: none"> • Characterized by two defects: <ol style="list-style-type: none"> 1. Insulin resistance: decreased ability of peripheral tissues to respond to insulin. The liver, skeletal muscle, and adipose tissue. 2. Beta cell dysfunction: that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.
Morphology	<ul style="list-style-type: none"> • Amyloid replacement of islets in long-standing type 2: deposition of pink, amorphous material. • Fibrosis at advanced stages.
Hyperosmolar Nonketotic coma	<ul style="list-style-type: none"> • Severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia. • Seen in older adult diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.

Chronic complications of DM

1. **Macrovascular Complications:** Atherosclerosis
2. **Microvascular Complications**
3. **Nephropathy:** 1. Glomerular lesion 2. Arteriosclerosis 3. Pyelonephritis
4. **Ocular Complications:** Retinopathy, cataract, glaucoma
5. **Diabetic neuropathy:** 1. Peripheral, symmetric 2. Autonomic 3. Diabetic mononeuropathy
6. **Infections:** 1. Renal papillary necrosis 2. Mucormycosis

Quiz

1) An infant is born following premature delivery. Multiple external congenital anomalies are noted. The infant exhibits a seizure soon after birth. The blood glucose is 19 mg/dL. Which of the following maternal diseases is the most likely cause for the observed findings in this infant?

- A- Cystic fibrosis
- B- Diabetes mellitus, type 2
- C- Gestational diabetes
- D- Maturity onset diabetes of the young

2) A 50-year-old man has had a nonhealing ulcer on the bottom of his foot for 2 months. On examination, the 2-cm ulcer overlies the right first metatarsal head. There is reduced sensation to pinprick in his feet. His visual acuity is reduced bilaterally. Laboratory studies show serum creatinine is 2.9 mg/dL. Which of the following laboratory test findings is he most likely to have?

- A- Glucosuria
- B- Hypoalbuminemia
- C- Hypokalemia
- D- Uricosuria

3) During Mid Morning, blood glucose levels fall and stimulate the secretion of which hormone?

- A- PTH
- B- Insulin
- C- Glycogen
- D- Glucagon

4) the risk factors for type 1 diabetes mellitus include:

- A- All of the options listed are correct.
- B- family history
- C- viral infection
- D- being overweight

5) A 35 year old patient comes to your clinic with newly diagnosed diabetes. Lab tests reveal no C-peptide in her blood. She has lost a lot of weight recently, despite the fact that she has been eating a lot. This patient has:

- A- adult-onset diabetes
- B- type 2 diabetes
- C- type 1 diabetes
- D- need more info

6) which of the following organism infection is highly predisposing to Diabetes mellitus?

- A- human immunodeficiency virus (HIV)
- B- coxsackie B virus
- C- cytomegalovirus
- D- B & C

7) Khalid, a 68 year-old civil engineer. BMI: 35, he has a history of poorly controlled DM over the last 20 years. 2 days ago he died of a stroke affected the brainstem.

What is suspected to see in pancreatic islets of Langerhans:

- A- Beta cells destruction by autoantibodies
- B- Insulinitis
- C- Islets replaced by Amyloid pink amorphous material
- D- nodular mesangial sclerosis

8) What are the genes involved in developing diabetes type 1?

- A- HLA-DR3.
- B- HLA-DR14.
- C- HLA-DR7.
- D- A&C

Thanks



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Done by the Dream Team

Special thanks to

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