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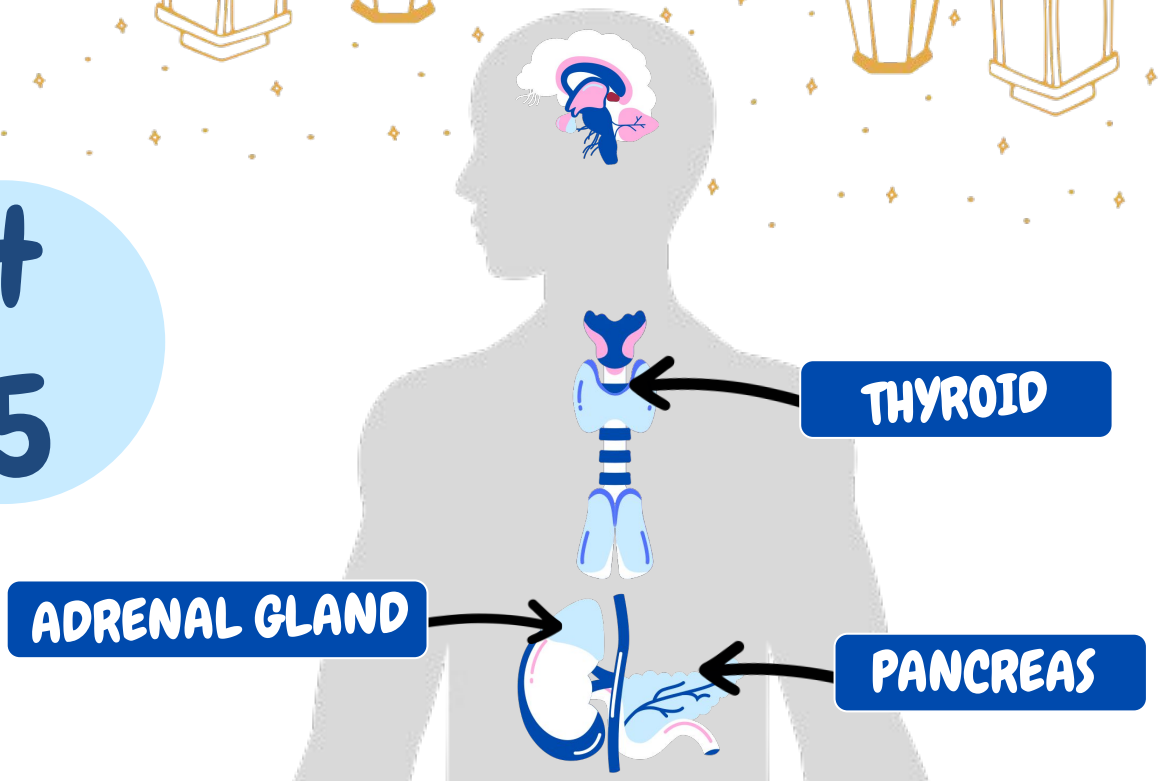

Diabetes mellitus
Types 1 & 2

Editing File

Color index :
Main text (black)
Female Slides (Pink)
Male Slides (Blue)
Important (Red)
Dr's note (Green)
Extra Info (Grey)

MED 443 King Saud University

ENDO BLOCK

Pathology Teamwork MED 443

Reviewed
Abdulaziz AlFuhayad
Mohammed AlEssa
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Objectives

To understand the structure of the pancreas and have a basic understanding of its function.

To understand the pathogenesis and major histopathological changes seen in diabetes mellitus type 1 and type 2.

The student should recognize the major complications of diabetes mellitus.

THIS LECTURE WAS PRESENTED BY DR.AMANY FATHADDIN & DR.MOHAMMED ALSWAYYED

لا تدع المذاكره تلهيك عن صلاة التراويح و قراءة القران الكريم

IF YOU WANT TO READ THE LECTURE FROM ROBBINS

IF YOU WANT TO READ THE LECTURE FROM FIRST AID

IF YOU WANT TO READ OSMOSIS SUMMARY

IF YOU WANT TO WATCH OSMOSIS ON DIABETES MELLITUS

Diabetes Mellitus

Definition

Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders sharing the common underlying feature of hyperglycemia.

Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or most commonly both.

Diabetes is the leading cause of end-stage renal disease, adult-onset blindness,and nontraumatic lower extremity amputations in USA

Prediabetes

Definition

Elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes .

1

persons with prediabetes have an elevated risk for development of frank diabetes

individuals with prediabetes have an elevated risk of cardiovascular disease.

2

3

As many as one-fourth of individuals with impaired glucose tolerance will develop overt diabetes in the next 5 years ,with additional risk factors such as obesity and family history compounding such risk.

Diabetes Mellitus

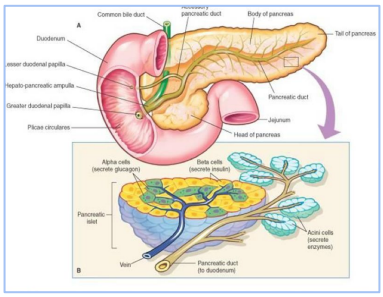
Diagnosis

مهم نعرف الأرقام هذه ليس فقط للباثو حتى للبايو و الفزيو

Blood glucose is normally maintained in a very narrow range, **70 to 120** mg/dL

	Diabetes mellitus	Prediabetes
Overview	According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diagnostic criteria for diabetes include the following:	Impaired glucose tolerance (prediabetes) is defined as:
1.Fasting plasma glucose	**≥ 126** mg/dL,and/or	**between 100 | 110 and 125** mg/dL("impaired fasting glucose"), and/or
2. Random plasma glucose	**≥200** mg/dL(in a patient with classic hyperglycemic signs, discussed later), and/or	-
2-hour plasma glucose	**≥ 200** during an oral glucose tolerance test (OGTT)with a loading dose of 75 gm, and/or	**between 140 and 199** mg/dL during an oral glucose tolerance test(OGTT), and/or
Glycated hemoglobin (HbA1C)	**≥6.5%**	**Between 5.7% and 6.4%**

Islets of Langerhans, contain four major cell type:	
β cell	Produces insulin
α cell	Secretes glucagon
δ cells	Contain somatostatin
PP cells (pancreatic polypeptide)	Contain a unique pancreatic polypeptide that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes



Diabetes Mellitus

Diagnosis

Females Slides

All tests, except the random blood glucose test in a patient with classic hyperglycemic signs, need to be repeated and confirmed on a separate day.

Of note, many 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 of diabetes requires persistence of hyperglycemia following resolution of the acute illness

Classification of DM

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

Modified from Diagnosis and classification of diabetes mellitus (American Diabetes Association). *Diabetes Care* 37:S81-S90, 2014.

1. Type 1 Diabetes	6. Endocrinopathies
Beta cell destruction, usually leading to absolute insulin deficiency	Growth hormone excess (acromegaly)
2. Type 2 Diabetes	Cushing syndrome
Combination of insulin resistance and beta cell dysfunction	Hyperthyroidism
3. Genetic Defects of Beta Cell Function	Pheochromocytoma
Maturity-onset diabetes of the young (MODY), caused by mutations in:	Glucagonoma
Hepatocyte nuclear factor 4α gene (*HNF4A*)—MODY1	7. Infections
Glucokinase gene (GCK)—MODY2	Cytomegalovirus infection
Hepatocyte nuclear factor 1α gene (*HNF1A*)—MODY3	Coxsackievirus B infection
Pancreatic and duodenal homeobox 1 gene (*PDX1*)—MODY4	Congenital rubella
Hepatocyte nuclear factor 1β gene (*HNF1B*)—MODY5	8. Drugs
Neurogenic differentiation factor 1 gene (*NEUROD1*)—MODY6	Glucocorticoids
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (3243A→G)	Thyroid hormone
Defects in proinsulin conversion	β-Adrenergic agonists
Insulin gene mutations	9. Genetic Syndromes Associated with Diabetes
4. Genetic Defects in Insulin Action	Down syndrome
Insulin receptor mutations	Klinefelter syndrome
5. Exocrine Pancreatic Defects	Turner syndrome
Chronic pancreatitis	10. Gestational Diabetes Mellitus
Pancreatectomy	Diabetes associated with pregnancy
Neoplasia	
Cystic fibrosis	
Hemochromatosis	
Fibrocalculous pancreatopathy	

Diabetes Mellitus

classification	
Type 1 DM	**Type 2 DM**
-Is an autoimmune disease characterized by pancreatic β-cell destruction and an absolute deficiency of insulin. -It accounts for approximately 5%-10% of all cases, and is the most common subtype diagnosed in patients younger than 20 years of age.	-Caused by a combination of peripheral resistance to insulin action+inadequate secretory\compensatory response by β cells ("relative insulin deficiency") -Approximately 90%-95% \80%-90% of diabetic patients have type 2, and many of them are overweight. -Although classically considered "adult-onset," the prevalence of type 2 in children+adolescents is increasing at an alarming pace due to increasing rates of obesity in these age groups.
Pathogenesis: -Is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens. -The classic manifestations of the disease occur late in its course, after > 90% of beta cells have been destroyed. -The Fundamental immune abnormality in type 1 is a failure of self-tolerance in T cells specific for Beta cell antigen -Autoantibodies against a variety of beta cell antigens ,are detected in blood of 70%-80% of patients -Genetic susceptibility :90%-95% of white patients with type 1 diabetes have **HLA-DR3, or DR4**. Several non-HLA genes also increase susceptibility to type 1 diabetes . -Environmental factors, especially infections, may be involved in type 1 diabetes.	**Pathogenesis**: -Type 2 diabetes is a prototypical \ heterogeneous and multifactorial complex disease that involves interactions of genetics,environmental risk factors such as a sedentary lifestyle and dietary habits. , and inflammation. recent large-scale genome-wide association studies, have identified more than a dozen susceptibility loci called "diabetogenic" genes. -Unlike type 1 diabetes, however ,there is **no** evidence of an autoimmune basis. The two defects that characterize type 2 diabetes: (1) a decreased ability of peripheral tissues to respond to insulin **(insulin resistance)** Decreased peripheral sensitivity to insulin (2) beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia

Diabetes Mellitus

Morphology

IMPORTANT

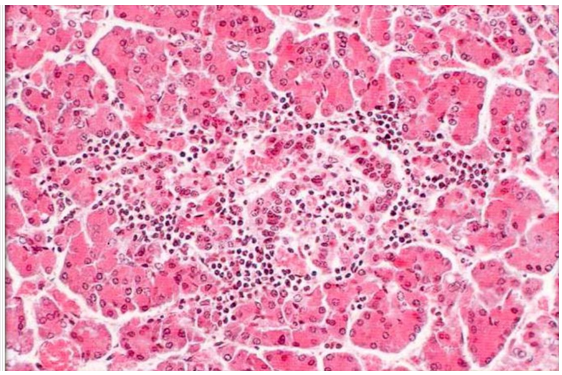
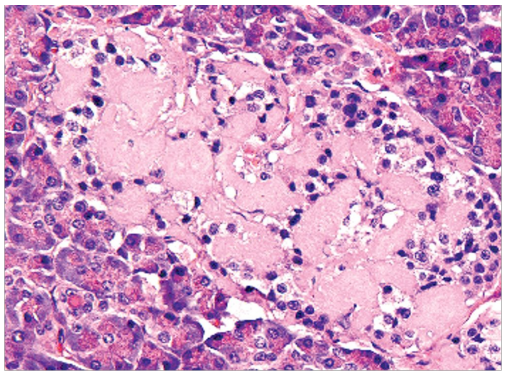
Lesions in the pancreas are inconstant and rarely of diagnostic value. One or more of the following alterations may be present:

- Reduction in the number and size of islets. This change most often is seen in **type 1 diabetes**.

- Leukocytic infiltration of the islets, (insulitis) are principally composed of mononuclear cells (lymphocytes and macrophages) T lymphocytes. They are most often seen **type 1 diabetes** at the time of clinical presentation.

- **Amyloid** replacement of islets in **long-standing type 2 diabetes,** appearing as deposition of pink, amorphous material. At advanced stages fibrosis also may be observed.

-An increase in the number and size of islets, especially characteristic of non diabetic newborns of diabetic mothers.

Insulitis	Amyloidosis
	

Deep Focus Question

What is FALSE about type 2 diabetes mellitus?

A. The disease is associated with a higher BMI.
B. The disease process most often occurs later in life.
C. It has a stronger genetic predisposition than type 1 DM.
D. DKA is the most common initial presentation.
E. The presence of prediabetes is a strong indicator of the development of disease.

Answer: D

Other Types of Diabetes

Monogenic Forms of Diabetes:	**Gestational** diabetes:
- Type 1 and type 2 diabetes are genetically complex, no single-gene defect (mutation) can account for predisposition to these entities. - By contrast, monogenic forms of diabetes are uncommon examples of the diabetic phenotype occurring as a result of loss-of-function mutations within a single gene. - Monogenic causes of diabetes include primary defects in beta cell function and insulin receptor signaling. - Monogenic diabetes can be classified based on age of onset into: **1** congenital early onset diabetes (manifesting in the neonatal period) **2 The largest subgroup of patients in this category traditionally was designated as having** maturity onset diabetes of the young MODY, because of its superficial resemblance to type 2 diabetes and its occurrence in younger patients which develops beyond the neonatal period but usually before 25 years of age. - MODY can be the result of inactivating mutations in one of six genes	- Pregnancy is a "diabetogenic" state in which the prevailing hormones favors a state of insulin resistance. In some euglycemic pregnant women this can give rise to gestational diabetes. - Women with pregestational diabetes (where hyperglycemia is already present in the periconceptional period) have an increased 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. - Develops in only a few percent of seemingly healthy women during pregnancy. It may continue after parturition in a small proportion of these patients. These women highly susceptible to overt T2DM later in life

Insulin Resistance

Definition

Failure of target tissues to respond normally to insulin.
Major tissues: Liver,skeletal muscle,adipose tissue are where insulin resistance manifests , It leads to decreased uptake of glucose in muscle, reduced glycolysis and fatty acid oxidation in the liver, and an inability to suppress hepatic gluconeogenesis.

Manifestations

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GLUCONEOGENESIS

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

GLUCOSE UPTAKE

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

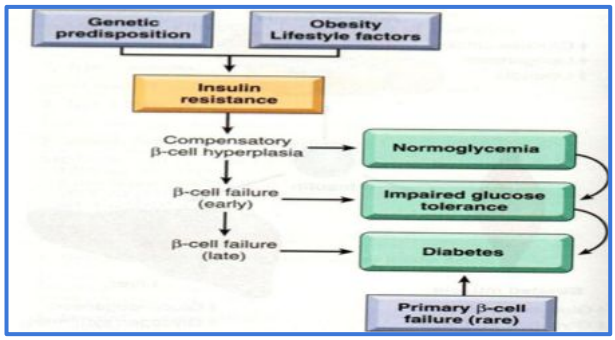
FREE FATTY ACIDS

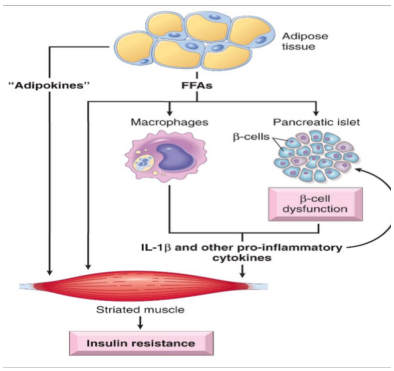
Failure to inhibit **hormone-sensitive lipase** in adipose tissue, leading to excess circulating free fatty acids (FFAs), which, exacerbates the state of insulin resistance

Obesity and Insulin Resistance

Females Slides

- The association of obesity with type 2 diabetes has been recognized for decades, with visceral obesity being common in a majority of affected patients.
- The term metabolic syndrome has been applied to a constellation of findings dominated by visceral obesity, accompanied by insulin resistance, glucose intolerance, and cardiovascular risk factors such as hypertension and abnormal lipid profiles.
- Individuals with metabolic syndrome are at high risk for the development of type 2 diabetes
- Central obesity (abdominal fat) is more likely to be associated with insulin resistance than is peripheral (gluteal/ subcutaneous) obesity





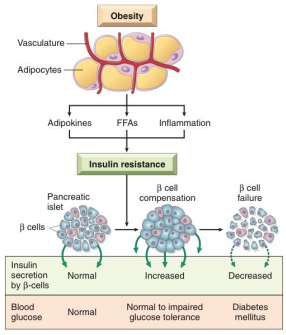


Fig. 20.23 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β cell compensation is followed by β cell failure, and diabetes ensues. *(Reproduced with permission from Kasuga M. Insulin resistance and pancreatic β-cell failure. J Clin Invest 116:1756, 2006.)*

early in the disease process, the islets show necrosis of beta cells and lymphocytic infiltration (so-called "insulitis", described later).

Females Slides

Insulin Resistance

Obesity and Insulin Resistance

Obesity can adversely impact insulin sensitivity by:

Excess FFAs: studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity. Intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state

Adipokines: Some of these promote hyperglycemia, and others (such as leptin and adiponectin) decrease blood glucose, by increasing the insulin sensitivity in the peripheral tissues. Adiponectin levels are decreased in obesity, thus 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 cytokine interleukin , as well as other cytokines promote insulin resistance in peripheral tissues.

Beta cell Dysfunction

While insulin resistance by itself can lead to impaired glucose tolerance, beta cell dysfunction is an essential component in the development of overt diabetes.442: Once there is beta cell dysfunction the patient is diabetic

442: Several mechanisms have been implicated in causing β cell dysfunction in type 2 diabetes, including the following:
- ↑↑FFA that compromise beta cell function and attenuate insulin release (lipotoxicity)
- Chronic hyperglycemia (glucotoxicity)
- Abnormal incretin effect → ↓ secretion of hormones that promote insulin release
- Amyloid replacement of islets.

Acute Complications

Overview

Females Slides

Type 1: Although beta cell destruction is a gradual process, the transition from impaired glucose tolerance to overt diabetes may be abrupt.

The onset of diabetes is marked by polyuria, polydipsia, polyphagia (known as the classic triad of diabetes), and in severe cases, **ketoacidosis**, all resulting from metabolic derangements.

The combination of polyphagia and weight loss is paradoxical and should always point to the possibility of diabetes.

The classic triad of diabetes: polyuria, polydipsia, and polyphagia.
Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness.

Complications

IMPORTANT

Type 1 DM "Diabetic Ketoacidosis"

➥ In patients with type 1 diabetes, deviations from normal dietary intake, unusual physical activity, infection, or any other forms of stress may rapidly influence/worsen the metabolic balance, predisposing the affected person/leading to diabetic ketoacidosis.

➥ The plasma glucose usually is in the range of 500 to 700 mg/dL.

➥ The marked hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state.

➥ The second major effect is activation of the ketogenic machinery. Insulin deficiency leads to excessive breakdown of adipose stores, giving rise to increased FFAs, which are oxidized by the liver to produce ketones as a source of energy for consumption. The rate at which ketones are formed may exceed the rate at which they can be used by peripheral tissues, leading to ketonemia and ketonuria.

➥ The accumulating ketones decrease blood pH, resulting in metabolic acidosis.

Type 2 DM "Hyperosmolar Non-ketotic Coma"

➥ Type 2 diabetes mellitus also may manifest with polyuria and polydipsia, but unlike in type 1 diabetes, patients often are older than 40 years and frequently are obese.

➥ In the decompensated state, patients with type 2 diabetes may develop hyperosmolar nonketotic coma.

➥ This syndrome is caused by severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia.

➥ Typically, the affected individual is an older adult diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.

Chronic Complications

Overview

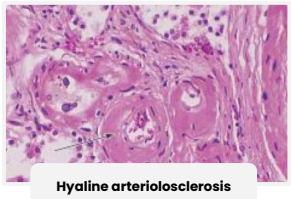
Females Slides

The morbidity associated with long-standing diabetes of any type results from the chronic complications of hyperglycemia, and the resulting damage induced in both:

- Large and Medium sized muscular arteries (Diabetic Macrovascular Disease).
- Small vessels (Diabetic Microvascular Disease).

1. Macrovascular Disease
2. Microangiopathy
3. Nephropathy
4. Ocular Complications
5. Neuropathy and Infections

Macrovascular Disease



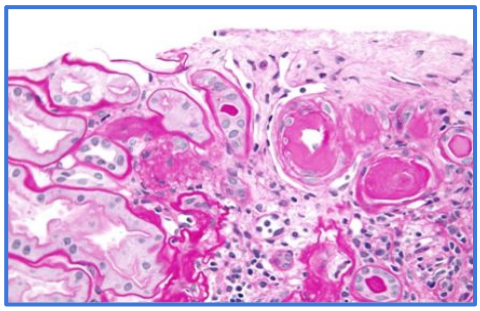
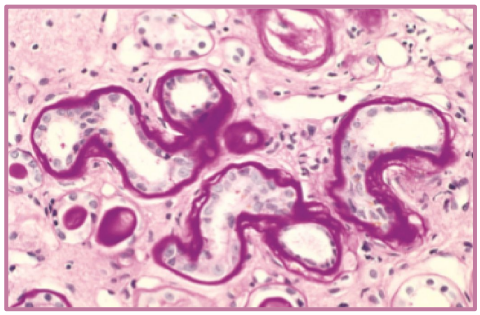
Hyaline arteriolosclerosis

- The hallmark of diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large and medium-sized arteries.
- Myocardial infarction, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics.
- Gangrene of the lower extremities, as a result of advanced vascular disease.
- The larger renal arteries also are subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation.
- Hyaline arteriolosclerosis, the vascular lesion associated with hypertension, is both more prevalent and more severe in diabetics than in non diabetics.
- It takes the form of an amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen.

Chronic Complications

1 Macrovascular Disease | 2 Microangiopathy | 3 Nephropathy | 4 Ocular Complications | 5 Neuropathy and Infections

Microangiopathy

Description	picture
One of the most consistent morphologic features of diabetes is **diffuse thickening of basement membranes.** The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla	
the basal lamina separating parenchymal or endothelial cells from the surrounding tissue is markedly thickened by concentric layers of hyaline material composed predominantly of type IV collagen . Of note, **despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.**	
The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.	

Nephropathy

Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered:

1. renal vascular lesions, principally arteriolosclerosis
2. glomerular lesions
3. pyelonephritis, including necrotizing papillitis.

Chronic Complications

Osmosis Vid

The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis.

IMPORTANT

GLOMERULAR CAPILLARY BASEMENT MEMBRANE

The glomerular capillary basement membranes are thickened along their entire length.

DIFFUSE MESANGIAL SCLEROSIS

consists of a diffuse increase in mesangial matrix along with mesangial cell . When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema

NODULAR GLOMERULOSCLEROSIS

ball-like deposits of a laminated matrix situated in the periphery of the glomerulus . These nodules are PAS-positive . This distinctive change has been called the Kimmelstiel-Wilson lesion.

Clinical Note

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are serious, acute complications of diabetes mellitus. DKA is characterized by hyperglycemia and ketoacidosis due to an absolute insulin deficiency. HHS is from a relative deficiency of insulin or insulin resistance, leading to severe hyperglycemia and elevated serum osmolality. Triggering factors include inadequate insulin therapy, underlying infection, concurrent medical illness, or drug side effects. Individuals with DKA tend to be younger, type 1 diabetics who present with acute symptoms.

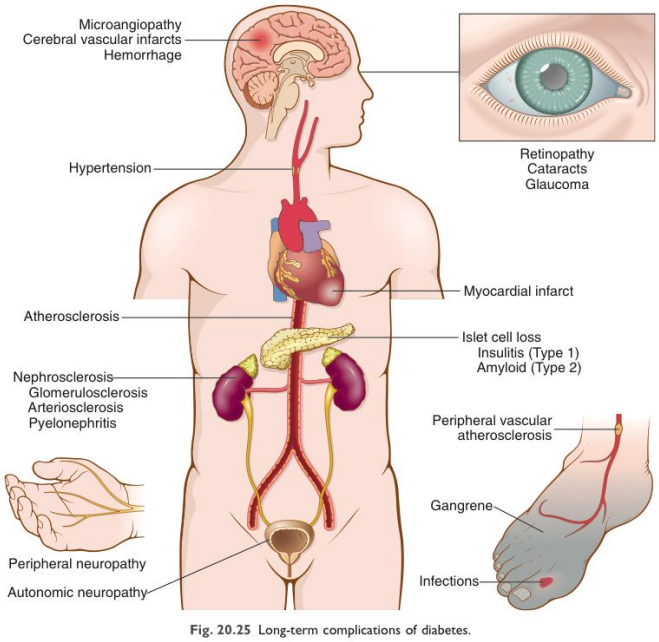


Fig. 20.25 Long-term complications of diabetes.

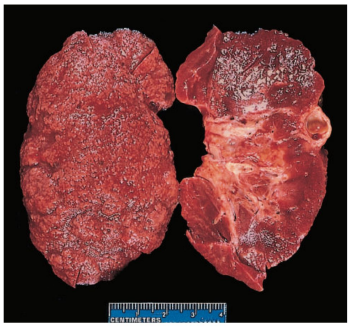
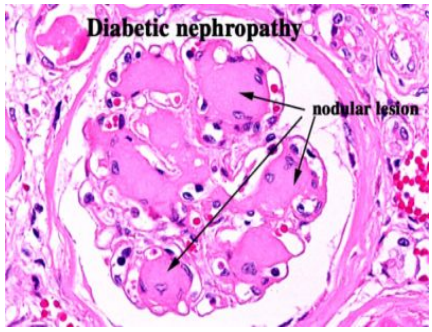
Females Slides

Chronic Complications

1 Macrovascular Disease | 2 Microangiopathy | 3 Nephropathy | 4 Ocular Complications | 5 Neuropathy and Infections

Diffuse and the nodular forms of glomerulosclerosis

- **In both slides:** Nodular glomerulosclerosis is encountered in approximately 15% to 30% of persons with long-term diabetes. It is essentially pathognomonic of diabetes.
- **In both slides:** Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular-appearing cortical surface

Grossly	Microscopically
 Fig. 20.31 Nephrosclerosis in a patient with long-standing diabetes. The bisected kidney demonstrates diffuse granular transformation of the surface *(left)* and marked thinning of the cortex *(right)*. Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst *(far right)*.	

Pyelonephritis

- is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to involve the tubules
- Both the acute and chronic forms of this disease occur in nondiabetics as well as in diabetics are more common in individuals with diabetes
- once affected, diabetics also tend to have more severe involvement.
- One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics.

Chronic Complications

1 Macrovascular Disease | 2 Microangiopathy | 3 Nephropathy | 4 Ocular Complications | 5 Neuropathy and Infections

Ocular Complications

- The ocular involvement may take the form of **retinopathy**, cataract formation or glaucoma.
- **Retinopathy is the most common pattern.**
- The lesion in the retina takes two forms :
  1- Nonproliferative (Background) retinopathy
  2- Proliferative retinopathy

IMPORTANT

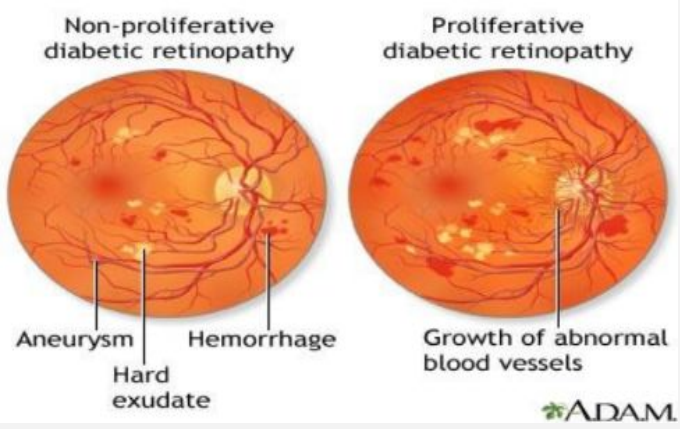
NONPROLIFERATIVE RETINOPATHY

Hemorrhages, retinal exudates (cotton wool sots) ,microaneurysm, venous dilations, edema, thickening of the retinal capillaries (microangiopathy) The retinal exudates can be "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids)

The microaneurysms are discrete saccular dilations of retinal choroidal capillaries that appear through the ophthalmoscope as small red dots.

PROLIFERATIVE RETINOPATHY

It's a process of neovascularization and fibrosis.
This leads to serious consequences, including blindness, especially if it involves the macula and retinal detachment.



Chronic Complications

1 Macrovascular Disease | 2 Microangiopathy | 3 Nephropathy | 4 Ocular Complications | 5 Neuropathy and Infections

Neuropathy

01

The central and peripheral nervous system are not spared by diabetes.

02

The most frequent pattern of involvement is that of a peripheral, symmetric neuropathy of the lower extremities affecting both motor and sensory function, particularly the latter.

03

Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop

04

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

Infections

- Diabetic patients have an enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis.
- Such infections cause about 5% of diabetes-related deaths.
- In a person with diabetic neuropathy, a trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death
- 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 infection 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

Diabetes Mellitus

Females Slides

Management

1. For **Type 1 Diabetes** : insulin replacement therapy is the mainstay of treatment.

2. Non Pharmacological approach such as : Dietary restrictions and exercise (which improves insulin sensitivity) are often the first line defense for patients with **Type 2 Diabetes** but most of them will eventually require therapeutic intervention to reduce hyperglycemia.

3. Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin (HbA1C) which is formed by nonenzymatic addition of glucose moieties to hemoglobin in the red cells.

4. Unlike blood glucose levels, HbA1C is a measure of glycemic control over long periods of time (2-3 months) and relatively unaffected by day-to-day variations. The ADA recommends maintenance of HbA1C levels less than 7% to reduce the risk of long-term complications

Deep Focus Question

What is a diagnostic criterion for diabetes mellitus?

A. Polyuria, polydipsia, and polyphagia with random glucose > 100 mg/dL
B. Hemoglobin A1c ≥ 6.5%
C. Random glucose > 200 mg/dL in an asymptomatic patient
D. Plasma glucose > 125 mg/dL 24 hours after an oral glucose load
E. Fasting glucose > 110 mg/dL on two separate occasions

Answer: B

Deep Focus Question

Which of the following chromosome and locus pairs are associated with type I diabetes mellitus?

A. Chromosome 6 - Major histocompatibility complex
B. Chromosome 17 - Formin homology 2 (FH2) domains
C. Chromosome 8 - Oculocutaneous albinism type 1
D. Chromosome 13 - Expansin gene family
E. Chromosome 10 - Hox family

Answer: A

Summary

Females Slides

Type 1 diabetes is an autoimmune disease characterized by progressive destruction of islet beta cells, leading to absolute insulin deficiency. Both autoreactive T cells and autoantibodies are involved.

• Type 2 diabetes is caused by insulin resistance and beta cell dysfunction, resulting in relative insulin deficiency. Autoimmunity is not involved.

• Obesity has an important relationship with insulin resistance (and hence type 2 diabetes), mediated by various factors, including excess free fatty acids, aberrant levels of adipokines, and an altered inflammatory milieu within adipose tissue.

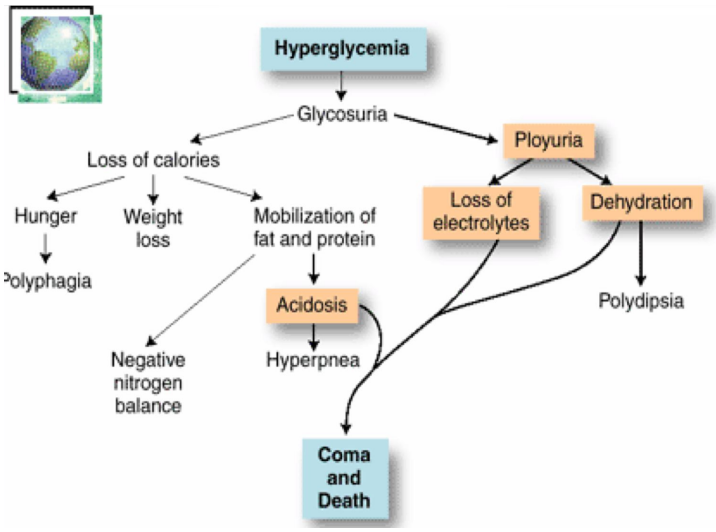
• Monogenic forms of diabetes are uncommon and are caused by single-gene defects that result in primary beta cell dysfunction or lead to abnormalities of insulin–insulin receptor signaling.

• The long-term complications of diabetes are similar in all types and affect mainly blood vessels, and the kidneys, nerves, and eyes.

Table 20.6 Type 1 Versus Type 2 Diabetes Mellitus

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset usually in childhood and adolescence	Onset usually in adulthood; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority of patients are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma
Genetics	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes
Pathogenesis	
Breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by beta cells Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Autoimmune "insulitis"	Amyloid deposition in islets (late)
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, Human leukocyte antigen; *MHC*, major histocompatibility complex.



	Fasting glucose	Non-Fasting glucose	Oral glucose tolerance	HbA1C
Note	Fasting for 8 hours	At anytime	Giving glucose and measured at intervals (usually 2 hours)	Glycated Hemoglobin (remember in GI?)
Prediabetes	**100 -125** mg/dL	-	**140 -199** mg/d	**5.7% -6.4%**
Diabetes	**≥ 126** mg/dL	**≥200** mg/dL	**≥200** mg/dL	**≥6.5%**

special thanks to Sultan Albaqami for this amazing table!!

Keywords

Diabetes Mellitus		• accelerated atherosclerosis causes Myocardial infarction • Gangrene • Hyaline arteriolosclerosis • diffuse thickening of basement membranes of vessels • Nephropathy due to renal vascular lesions by arteriolosclerosis • Diffuse mesangial sclerosis • Nodular glomerulosclerosis : Kimmelstiel-Wilson lesion. • Pyelonephritis : necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics. • retinopathy , cataract formation or glaucoma , blindness • Nonproliferative retinopathy : Hemorrhages, retinal exudates (cotton wool sots) • Proliferative retinopathy is a process of neovascularization and fibrosis. • Neuropathy : peripheral symmetric neuropathy of lower limbs • foot drop Or wrist drop • Mucormycosis : fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain
	Diabetes Mellitus Type 1	• Autoimmune disease characterized by pancreatic β-cell destruction • absolute deficiency of insulin. • failure of self-tolerance in T cells specific for Beta cell antigen • HLA-DR3, or DR4 • Children onset mostly • Reduction in the number and size of islets. • Leukocytic infiltration of the islets, (insulitis) are principally composed of T lymphocytes. • Diabetic Ketoacidosis (plasma glucose : 500 to 700 mg/dL.)
	Diabetes Mellitus Type 2	• combination of peripheral resistance to insulin action+ inadequate secretory • overweight • adult-onset Mostly • Amyloid replacement of islets & fibrosis • Hyperosmolar Nonketotic Coma caused by severe dehydration
	Monogenic Forms of Diabetes	• loss-of-function mutations within a single gene. A. congenital early onset diabetes (manifesting in the neonatal period) B. maturity onset diabetes of the young MODY : develops beyond the neonatal period but usually before 25 years of age.
	Gestational diabetes	• Pregnancy • Lead to Fetal overgrowth (macrosomia)
Insulin Resistance		• Failure of target tissues to respond normally to insulin. • Failure to inhibit Gluconeogenesis • Failure to inhibit hormone-sensitive lipase • Central obesity • Excess FFAs • Adipokines , leptin , adiponectin , promote hyperglycemia

IF YOU WANT A SUMMARY CLICK HERE

MCQs

Question 1

What is associated with type 1 diabetes mellitus?

A. HLA-B27

B. HLA-B17

C. HLA-Q19

D. HLA-DR3 and 4

Question 2

What is NOT a microvascular complication of diabetes mellitus?

A. Nephropathy

B. Cerebrovascular disease

C. Retinopathy

D. Neuropathy of the entire hand

Question 3

What is NOT a feature of type I diabetes mellitus?

A. Beta-cell destruction in pancreatic islet cells

B. Initial diagnosis before 30 years of age

C. HLA link & DKA

D. Increased insulin resistance

Question 4

What is the most common complication of diabetes mellitus?

A. End-stage liver disease

B. Chronic renal failure

C. Coronary artery disease

D. CVA

1-D \ 2–B \ 3-D \ 4-B

MCQs

Question 5

Which of the following differentiates diabetes mellitus from diabetes insipidus?

A. Polyuria
B. Hyperglycaemia
C. Hypernatremia
D. Hyperkalemia

Question 6

What material is deposited within the pancreatic islets in advanced type 2 diabetes mellitus?

A. Tau
B. Amyloid
C. Mutated glucagon
D. Phospholipase A

Question 7

The pathophysiology of diabetes mellitus type 1 involves...

A. the narrowing of the pancreatic duct
B. the generation of autoantibodies against pancreatic islet cells.
C. pancreatic fibrosis.
D. the narrowing of the common bile duct.

Question 8

Which of the following is the cutoff of HbA1c for diagnosing type 2 diabetes mellitus?

A. 5.7%
B. 5.5%
C. 8.0%
D. 6.5%

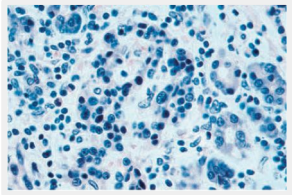
5-B \ 6-B \ 7-B \ 8-D

Cases

1.A 14-year-old boy presents for a pre summer camp physical examination. Routine urinalysis discloses 3+ glucosuria. He admits to thirst and frequent urination, accompanied by a4-kg (9-lb) weight loss over the past few months. His parents note that he had a flu-like illness 5 months ago. His blood glucose is 220 mg/dL. Which of the following best explains the pathogenesis of hyperglycemia in this patient?

A.Increased peripheral insulin uptake	B.Irregular insulin secretion	C.Islet cell destruction	D.Peripheral insulin resistance

2.A 10-year-old boy with a recent onset of diabetes mellitus dies following an automobile accident. Histologic examination of the child's pancreas at autopsy is shown in the image. Injury to pancreatic islet cells in this patient was most likely mediated by which of the following mechanisms of disease?



A.Antibody-mediated islet cell destruction	B.Cell-mediated immunity	C.Direct viral cytopathic effects	D.Hypovolemic shock

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 findings 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

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.Increased insulin uptake	C. Peripheral Neuropathy	D. Vasculitis

5.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

1-C \ 2–B \ 3-D \ 4-A \ 5-A

NEED EXPLANATION ? CLICK HERE

Cases

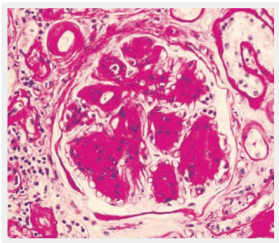
6.A 65-year-old obese man (body mass index = 32 kg/m2) presents with a 2-year history of difficulty walking. Physical examination reveals chronic ulcers in the lower extremities. Funduscopic examination reveals proliferative retinopathy. Which of the following best describes the pathogenesis of chronic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

A.Inadequate leukocytic response to infection	B.Low concentrations of insulin in tissues	C.Microvascular disease	D.Varicose veins

7.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?

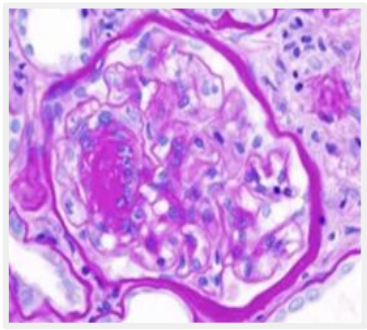
A.Amyloidosis	B.Glycosylation	C.Immunoglobulin deposition	D.Insudation of fibrin

8.A 50-year-old man with diabetes mellitus develops swelling in his lower extremities. Urinalysis shows 3+ proteinuria and 3+ glucosuria. Serum albumin is 3 g/dL and serum cholesterol is 350 mg/ dL. A kidney biopsy is shown in the image. Which of the following glomerular changes is evident in this biopsy specimen?

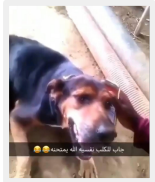


A.Amyloidosis	B.Deposition of basement membrane like material	C.Endothelial cell hyperplasia	D.Fibrinoid necrosis

9.A 62-year-old woman comes to the clinic due to progressive fatigue, weight loss, and ankle swelling for the past two months. Physical examination shows 2+ pitting edema around the ankles. Cardiovascular and respiratory examinations are non-contributory. Laboratory results show a serum creatinine level of 3.1 mg/dL, albumin of 2.2 g/dL, and total cholesterol concentration of 290 mg/dL. Urinalysis results show 3+ proteinuria without hematuria or red cell casts. Renal biopsy is performed, and the results are shown below: Which of the following is the most likely explanation for this patient's condition?



A..Diffuse proliferative glomerulonephritis	B.Diabetic glomerulonephropathy	C.Membranous nephropathy	D.none



سألناك فيها بالضبط بالريتال
و رجعنا نسألها الحين

6-C \ 7–B \ 8-B \ 9-B

NEED EXPLANATION ? CLICK HERE

Cases

EXTRA CASES MAY REQUIRE EXTRA INFO

1.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
2.A 75-year-old woman with well-controlled diabetes complains of poor eyesight. A grayish-white opacification 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
3. 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

Last Lecture Icons !

1-A \ 2–A \ 3-C

Pathology Team

Leader
زياد العتيبي

Leader
لمى العتيبي

- رغد المصلح
- محمد العرفج
- عائشة إبراهيم
- ريما المطيري
- دينا المهوس
- أفنان الأحمري
- دانه المحيسن
- فيصل الشويعر
- ليان الرويلي
- عروب المحمود
- ألين الكلية
- إيلاف معتبي
- عبدالمحسن الدايل
- رند اباالخيل
- نوره المحيميد
- يزيد المطيري
- رزان السطيحي
- سلطان البقمي
- ريماز المحمود
- يزيد آل طلحه
- شوق الخليفة
- لؤي الحديثي
- ساره العجاجي
- معاذ الحضيف
- الجوهرة الوهيبي