جامعة الملك سعود
King Saud University

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Any future corrections will be in the editing file , Click

Pathology

Diabetes mellitus

439

Color index
- Important
- Doctor's note
- Extra info
- Main text
- ★ Male's slide
- ★ Female's slide

Revised & Approved
Bassam Alasmari
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" اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا "

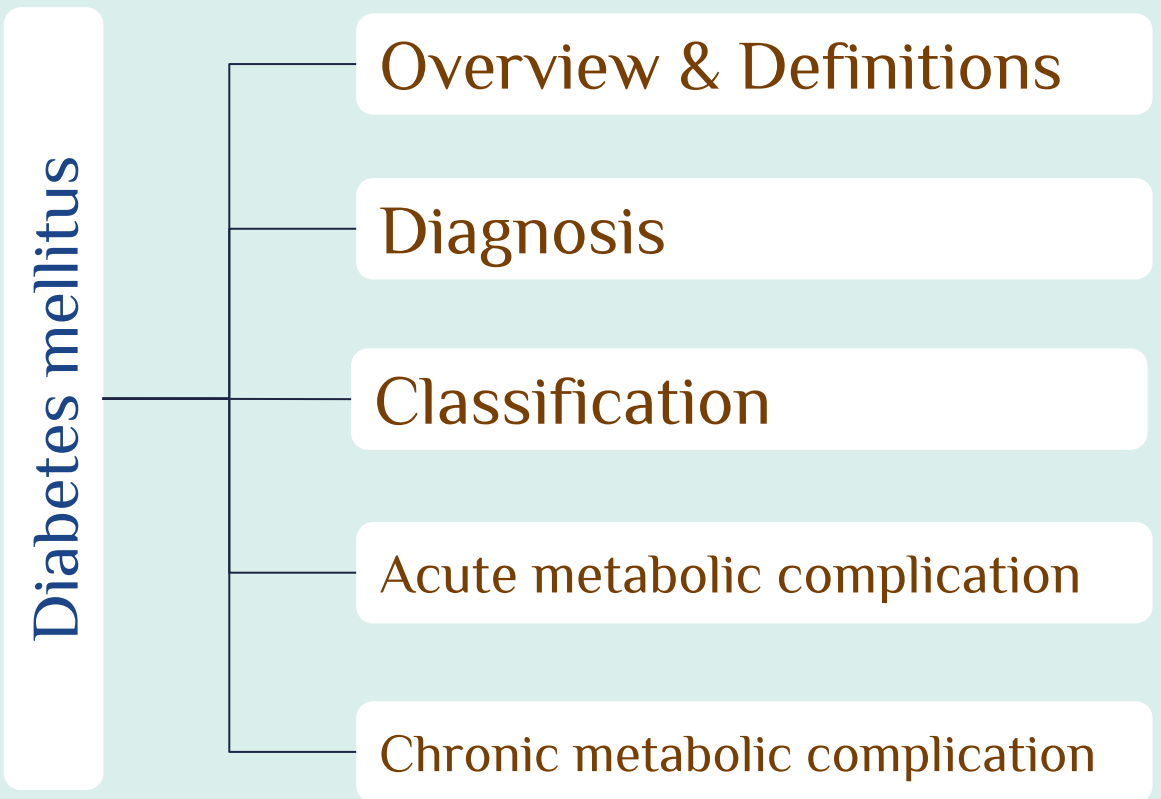
Objective

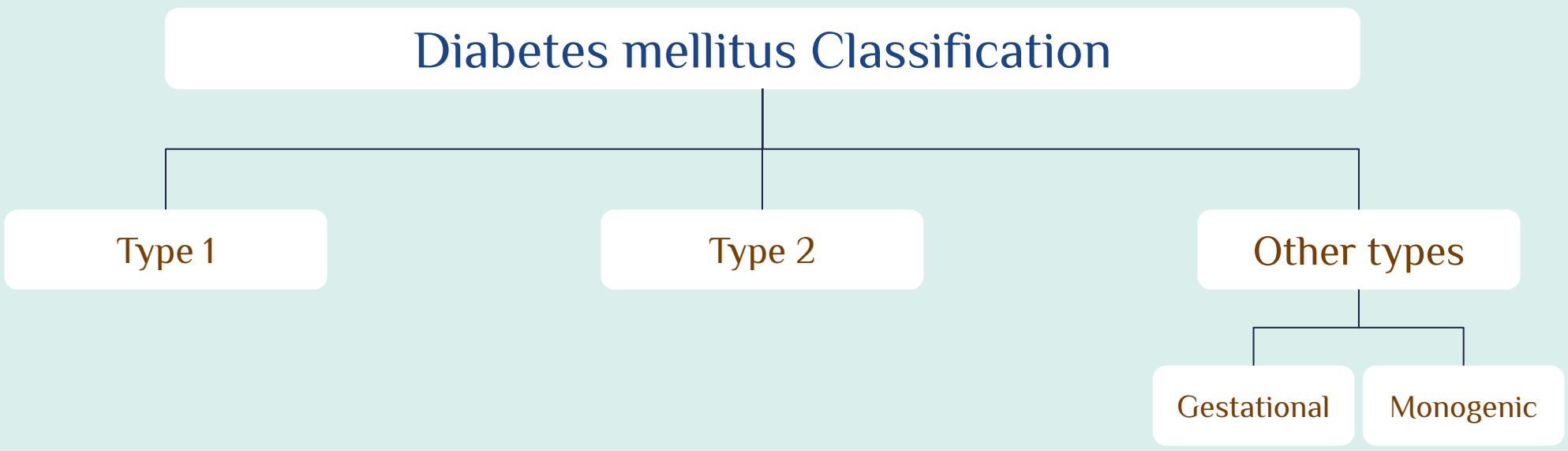
01 To understand the structure of the pancreas and have a basic understanding of its function.

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

03 To recognize the major complications of diabetes mellitus.

Overview





Diabetes Mellitus

Islets of Langerhans, contain four major cell types:

1. β cell → Produces **insulin**
2. α cell → Secretes glucagon
3. δ cells → Contain somatostatin
4. PP cells → Contain a unique pancreatic polypeptide that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes

Diabetes Mellitus

- 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 (destruction of β cells of the pancreas), insulin action, or most commonly both.
- Diabetes is the leading cause (number 1 cause) of end-stage renal disease, adult- onset blindness, and nontraumatic lower extremity amputations in USA

...e 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

...odified from Diagnosis and classification of diabetes mellitus (American Diabetes ...iation). *Diabetes Care* 37:S81-S90; 2014.

Prediabetes

- Defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes. persons with prediabetes have an elevated risk for development of frank diabetes.
- 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

	Diabetes Mellitus (DM)	Prediabetes
Diagnosis	❖ **Blood glucose is normally maintained in a very narrow range, usually 70 to 120 mg/dL** ❖ 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 (at any time) plasma glucose greater than or equal to 200 mg/dL (in a patient with classic hyperglycemic signs, discussed later), 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(we give the patient 75g of glucose, after 2 hours we measure the blood glucose level), and/or 4) A glycated hemoglobin (HbA1C) level greater than or equal to 6.5% (glycated Hb is further discussed under chronic complications of diabetes)	❖ **Impaired glucose tolerance (prediabetes) is defined as:** 1) A fasting plasma glucose between 100 and 125 mg/dL ("impaired fasting glucose"), 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%
Complications	Diabetes is the leading cause of: ❖ End-stage renal disease ❖ Adult- onset blindness ❖ Nontraumatic lower extremity amputations in USA	Individuals with prediabetes have an elevated risk of cardiovascular disease.

- ❖ 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. So we don't label the patient as diabetic after the first result, we have to do the test again to confirm the diagnosis except if he has all the signs & symptoms with the elevated blood glucose level .
- ❖ 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.That's why we repeat the test on a separate day to confirm the diagnosis .
- ❖ The diagnosis of diabetes requires persistence of hyperglycemia following resolution of the acute illness

Type 1 Diabetes (T1DM)

Overview

Type 1 diabetes is an **autoimmune** disease characterized by **pancreatic β-cell destruction** by T-lymphocytes leading to an **absolute deficiency of insulin**. It accounts for approximately 5% to 10% of all cases, and is the most common subtype diagnosed in patients younger than 20 years of age.

Insulin deficiency leading to metabolic disorders characterized by **hyperglycemia** due to autoimmune destruction of beta cells **by T lymphocytes.**

1. characterized by inflammation of islets
2. associated with HLA-DR3,4
3. autoantibodies against insulin often present and may be seen years before clinical disease develops

Manifests in childhood with clinical features of insulin deficiency

1. High serum glucose-Lack of insulin leads to decreased glucose uptake by fat and skeletal muscles.
2. Hyperglycemia exceeds renal ability to reabsorb glucose, excess filtered glucose leads to osmotic diuresis which leads to polyuria, polydipsia and glycosuria.

What are the risk factors that trigger type I DM ?

Nothing for sure, but genetic susceptibility and environmental factors (certain viral infections, some of the viral components mimic some of this type of tissue present in beta cells) play a role (which means it is multifactorial). But the basis is **autoimmune disease**

Pathogenesis

- Type 1 diabetes 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 more than 90% of the beta cells have been destroyed (Gradual loss of **β** cells until 90% of them have been destroyed)
- The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells specific for Beta cell antigens.

1 Genetic susceptibility

90% and 95% of white patients with T1DM have **HLA-DR3, or DR4**. or both However, most individuals who have these HLA alleles do not develop diabetes, indicating that these genes contribute to the disease but do not cause it by themselves. Several non-HLA genes (as CTLA4) also increase susceptibility to type 1 diabetes. (There is no one single gene mutation associated with type I DM).

2 Environmental factors

Especially infections (viruses such as Mumps, Rubella and Coxsackie B viruses) Perhaps because some viral antigens mimic beta cell antigens leading to autoimmune destruction of the islets.

3 Autoantibodies

Against a variety of beta cell antigens, including insulin are detected in the blood of 70% to 80% of patients.

Type 2 Diabetes (T2DM)

Overview

- ❖ Type 2 diabetes is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells (“relative insulin deficiency”).
- ❖ Approximately 90% to 95% of diabetic patients have type 2 diabetes, and many of them are overweight (obesity leads to decreased numbers of insulin receptors).
- ❖ Although classically considered “adult-onset,” the prevalence of type 2 diabetes in children and adolescents is increasing at an alarming pace due to the increasing rates of obesity in these age groups (It is diagnosed in younger age groups because of increasing rates of obesity)

❖ **2 factors are associated with this type of diabetes:**

1. Factor 1 : Normally, action of insulin is on the liver, skeletal muscles and adipose tissue which have certain receptors the insulin binds to, resulting in facilitating the transfer of glucose from the blood to these cells. In type II diabetics, the insulin levels are normal but not functioning properly (due to insulin resistance from these peripheral tissues).
2. Factor 2 : Inadequate secretory response by pancreatic beta cells (not absolute deficiency) we call it **relative** insulin deficiency.

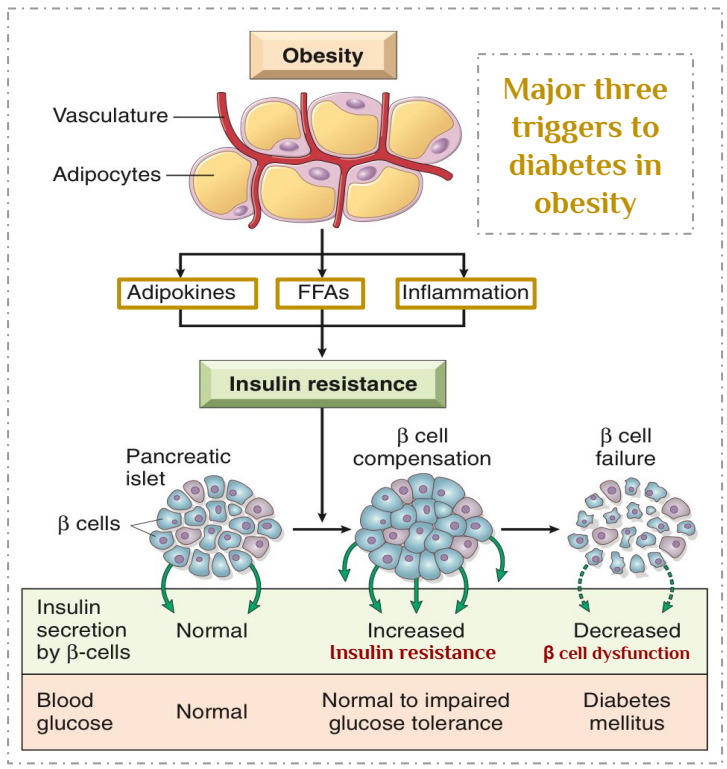
Pathogenesis

Type 2 diabetes is a heterogeneous and multifactorial complex disease that involves interactions of **genetics**, **environmental risk factors**, and **inflammation**. Unlike type 1 diabetes, however, there is no evidence of an autoimmune basis.

❖ **The two defects that characterize type 2 diabetes are:** (further explained next slide)

1. **Insulin resistance**: A decreased ability of peripheral tissues to respond to insulin .
2. **Beta cell dysfunction:** Manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.

- ❖ Often accompanied with compensatory beta cell hyperfunction and hyperinsulinemia in early stages. environmental factors such as sedentary lifestyle and dietary habits play a role in the development of the disease.
- ❖ Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue.
- ❖ Pancreatic cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, cell compensation is followed by cell failure, and diabetes.



Insulin resistance

Insulin resistance is defined as the failure of target tissues to respond normally to insulin. The liver, skeletal muscle, and adipose tissue are the major tissues.

manifests as follows:

- Failure to inhibit endogenous glucose production (gluconeogenesis) in the liver, which contributes to high fasting blood glucose levels (During fasting, If there's no action of insulin, the liver will produce glucagon which antagonize the action of insulin leading to increased gluconeogenesis and elevated fasting blood glucose levels)
- Abnormally low glucose uptake and glycogen synthesis in skeletal muscle **following a meal**, which contributes to a high postprandial blood glucose level
- Failure to inhibit hormone-sensitive lipase in adipose tissue, leading to excess circulating free fatty acids (FFAs), which exacerbates the state of insulin resistance (↑ lipolysis, these FFAs have -ve effect on insulin leading to increased insulin resistance)

Obesity and Insulin Resistance

- 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 (depends on fat distribution)
- Central obesity (abdominal fat) is more dangerous because it is more likely to be associated with insulin resistance than is peripheral (gluteal/ subcutaneous) obesity.
- Guyton: studies suggest that obese subjects have fewer insulin receptors, especially in the skeletal muscle, liver, and adipose tissue, than do lean subjects

- **Obesity can adversely impact insulin sensitivity by:**

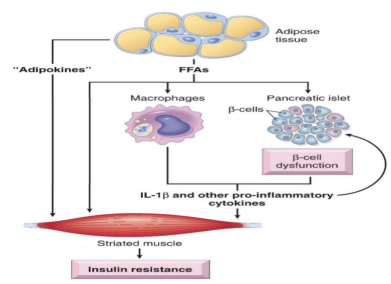
Excess FFAs:	Studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity. So obesity → excess FFAs → -ve effect on insulin action → insulin resistance state
Adipokines:	Some of these promote hyperglycemia, and others (such as **leptin and adiponectin**) decrease 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. It will start with insulin resistance and end with beta cells dysfunction. Once there's beta cell dysfunction the patient is diabetic .

Several mechanisms have been implicated in causing beta cell dysfunction in type 2 diabetes, including the following:

- Excess free fatty acids that compromise beta cell function and attenuate insulin release(lipotoxicity)
- Chronic hyperglycemia (glucotoxicity)
- Abnormal incretin effect, leading to reduced secretion
- of hormones that promote insulin release.
- Amyloid replacement of islets.



Morphology

Females' dr: It is **Important** to differentiate between the morphological criteria in each type

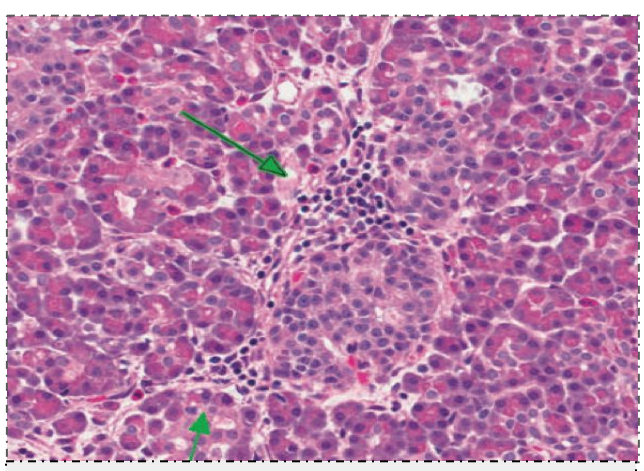
- Lesions in the pancreas are inconstant and rarely of diagnostic value. One or more of the following alterations may be present:

01 **Leukocytic infiltration of the islets (insulitis)**
Are principally composed of **T lymphocytes**. They are most often seen **type 1** diabetes at the time of clinical presentation

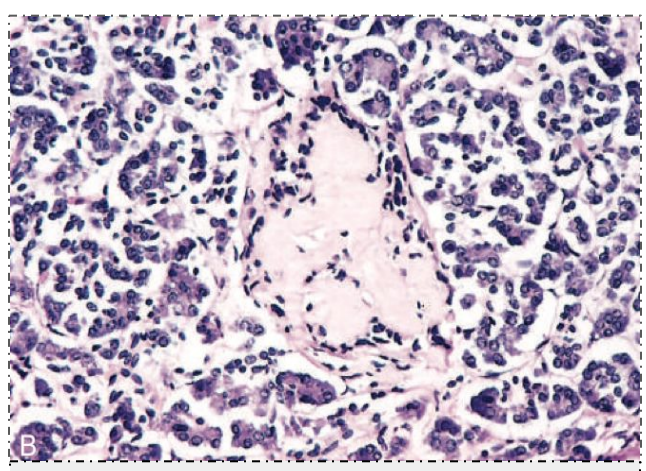
02 **Amyloid replacement of islets** in long-standing **type 2** diabetes, appearing as deposition of pink, amorphous material. At advanced stages **fibrosis** also may be observed .

03 **Reduction in the number and size of islets.** This change most often is seen in **type 1** diabetes. Because of the destruction of beta cells.

04 **An increase in the number and size of islets**, especially characteristic of nondiabetic newborns of diabetic mothers. Babies (whose mothers are diabetics) will have increased number and size of islets of langerhans because of the elevated blood glucose coming from the mother. So beta cells will increase in size and number to secrete more insulin.



Insulitis in type I DM



Amyloidosis in type II DM

Other types of diabetes

Monogenic Forms of 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:

Congenital early onset diabetes (manifesting in the neonatal period)

Maturity onset diabetes of the young (MODY), which develops beyond the neonatal period, but usually before 25 years of age.

Gestational diabetes

- **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.

- Complications of gestational diabetes: Fetal overgrowth (macrosomia) occurs because maternal hyperglycemia can induce compensatory secretion of insulin-like growth factors in the fetus.

Acute Metabolic Complication of Diabetes

Complications that make the patients come to ER

Overview

- 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 (frequent urination)**, **polydipsia (thirst)**, **polyphagia** (known as the classic triad of diabetes), and in severe cases, ketoacidosis, all resulting from metabolic derangements. **Polyuria** : because the kidneys are trying to get rid of the excessive glucose (can't reabsorb it anymore), water will be excreted too with the glucose leading to frequent urination that results in increased osmolality activating hypothalamic receptors that send signals to drink more water (**polydipsia**). **Polyphagia** : because the insulin action isn't taking place (the building up/anabolic action is absent) that's why the body responds by polyphagia which means the patient needs to eat more. However, there's **no weight gain** with the polyphagia because of the absence of the anabolic action of insulin hormone and due to the breaking down of fats and proteins in skeletal muscles.

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

Diabetic Ketoacidosis (Type 1)

- In type 1 diabetes: significant deviations from normal dietary intake, unusual physical activity, infection or any forms of stress, which normally results in the release of catecholamines and cortisol that antagonize insulin action inducing the liver to produce more glucose, may worsen the metabolic imbalance, leading to diabetic ketoacidosis. The plasma glucose usually is in the range of 500 to 700 mg/dL (very high)
- Absolute insulin deficiency and unopposed effects of counter regulatory hormones (epinephrine, glucagon)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 activation of hormone-sensitive lipase, with 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 by vital organs (e.g., the brain). 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.
- **Characteristic features of ketoacidotic state :**
  1- Dehydration
  2- **very high** glucose level in the blood
- Keto = increased ketones level in blood and urine
- Acidosis = low blood pH

Hyperosmolar Non-ketotic Coma (Type 2)

- patients with type 2 diabetes may develop hyperosmolar nonketotic coma.
- Old patients who have no enough fluid intake will have severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia. Usually the blood glucose level is not very well controlled so they always have diuresis.
- 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.
- The absence of ketoacidosis and its symptoms (nausea, vomiting, respiratory difficulties) delays recognition of the seriousness of the situation until the onset of severe dehydration and coma.

Chronic Metabolic Complication of Diabetes

- 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 **(Diabeteic macrovascular disease)**
  - Small-vessel **(Diabetic microvascular disease)**

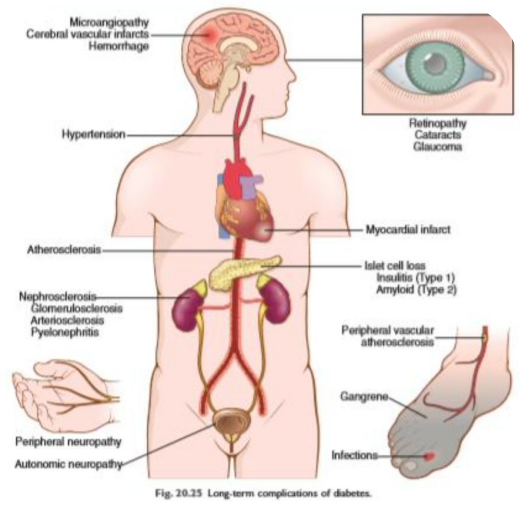
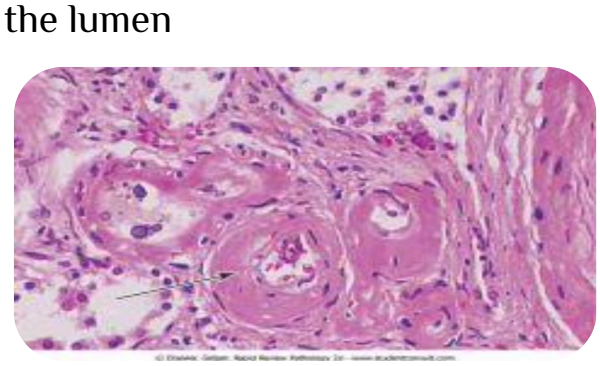


Fig. 20.25 Long-term complications of diabetes.

1. Macrovascular Disease

- 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 or any ischemic heart disease, is the most common cause of death in diabetics
- Gangrene of the lower extremities, as a result of advanced vascular disease (diabetic foot may lead to its amputation)
- 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



2. Microangiopathy

- 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** (abnormalities in the microcirculation that supply the glomeruli, tubules and medulla), **retinopathy**, and some forms of **neuropathy**.

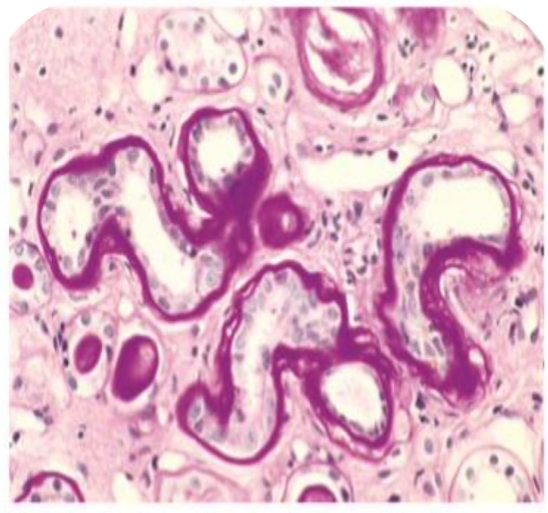


Fig. 20.28 Renal cortex showing thickening of tubular basement membranes in a specimen from a diabetic patient. (Periodic acid–Schiff stain.)

Used to evaluate the basement membrane thickness

Chronic Metabolic Complication of Diabetes

2.1. Nephropathy

- Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered:
  - Glomerular lesions; called glomerulitis
  - Renal vascular lesions, principally arteriolosclerosis
  - Pyelonephritis, including necrotizing papillitis. Inflammation of kidneys, not specific for diabetes but diabetics have increased risk

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

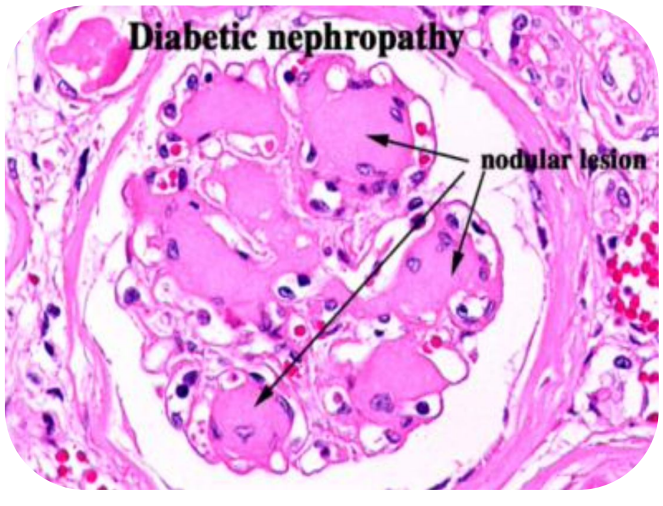
- The glomerular capillary basement membranes are thickened along their entire length.

- **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**.

- Nodular glomerulosclerosis is encountered in approximately 15% to 30% of persons with long-term diabetes. It is essentially pathognomonic of diabetes.

- 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**



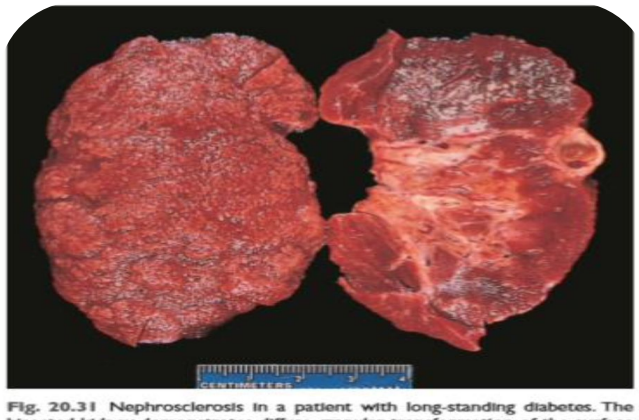


Fig. 20.31 Nephrosclerosis in a patient with long-standing diabetes. The bisected kidney demonstrates diffuse granular transformation of the surface *(left)* and marked thinning of the cortex *(right)*. Additional features include some irregular depressions, the result of pyelonephritis, and an incidental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

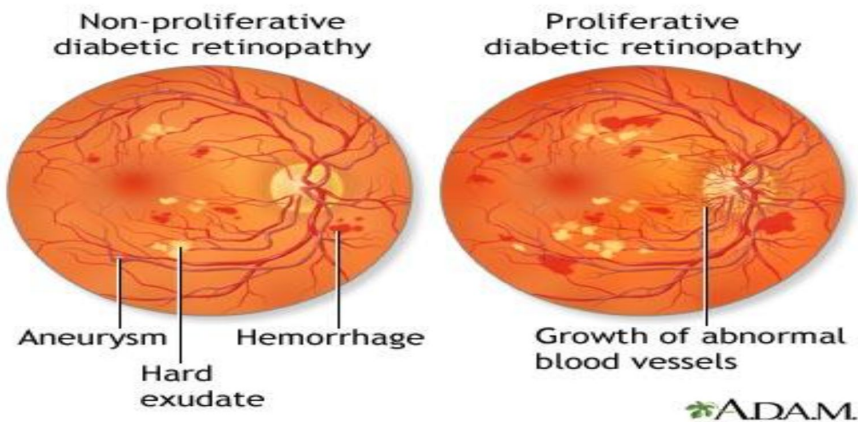
- Pyelonephritis is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to involve the tubules. Both the acute and chronic forms of this disease occur in non diabetics as well as in diabetics are more common in individuals with diabetes, and 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 non diabetics.

Chronic Metabolic Complication of Diabetes

2.2. Ocular Complications

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



- **Nonproliferative retinopathy:**

Includes hemorrhages, retinal exudates, microaneurysms, venous dilations, edema, and, most importantly, **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:**

Proliferative retinopathy is a process of **neovascularization** and **fibrosis**.

This lesion leads to serious consequences, including blindness, especially if it involves the macula and retinal detachment

2.3. Neuropathy

- The central and peripheral nervous systems are not spared by diabetes.
- The most frequent pattern of involvement is that of a peripheral, symmetric (right & left) neuropathy of the lower extremities affecting both motor and sensory function, particularly the latter.
- Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and diabetic mononeuropathy (one nerve is affected) , which may manifest as sudden **footdrop** or **wristdrop** .
- Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.

3. 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** fungal 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.

Diabetes Management

- For patients with type 1 diabetes, insulin replacement therapy is the mainstay of treatment, while nonpharmacologic approaches such as dietary restrictions and exercise (which improves insulin sensitivity) are often the “first line of defense” for type 2 diabetes.

- Most patients with type 2 diabetes eventually require therapeutic intervention to reduce hyperglycemia.

- Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin, also known as HbA1C, which is formed by nonenzymatic addition of glucose moieties to hemoglobin in red cells.

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

QUIZ!

MCQs

01 | The _____ _____ secrete insulin which are located in the _____.			
A) Alpha cells, liver	B) Alpha cells, pancreas	C) Beta cells, liver	D) Beta cells, pancreas
02 | Diabetes is defined best as...			
A) A metabolic disease characterized by low blood sugar	B) A metabolic disease characterized by high blood sugar	C) A family of blood infections	D) None of the above
03 | Gestational diabetes occurs..			
A) During pregnancy	B) At birth	C) After menopause	D) Before pregnancy
04| What statement is INCORRECT regarding Diabetic Ketoacidosis?			
A) DKA occurs mainly in Type1	B) Ketones are present in the urine in DKA.	C) Severe hypoglycemia is a hallmark sign in DKA.	D) Options C & A
05 | A Type 2 diabetic may have all the following signs or symptoms EXCEPT:			
A) Glycosuria	B) Ketones present in the urine	C) polyuria	D)polydipsia
06 | Amyloidosis seen in which of the following ?			
A) IDDM	B) T2DM	C) Gestational diabetes	D) Monogenic Forms of Diabetes
07 | A 60-year-old man with diabetes mellitus complains of deep burning pain and sensitivity to touch over his hands and fingers. Nerve conduction studies show slow transmission of impulses and diminished muscle stretch reflexes 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 Deficiency	D) Ketoacidosis
08 | 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

MCQs Answer key	01	02	03	04	05	06	07	08
	D	B	A	C	B	B	B	A

This summary was taken from Robbins

Summary

DIABETES MELLITUS: PATHOGENESIS AND LONG- TERM COMPLICATIONS

- 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. The development of these complications is attributed to three underlying mechanisms: formation of AGEs, activation of PKC, and disturbances in polyol pathways leading to oxidative stress.

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.

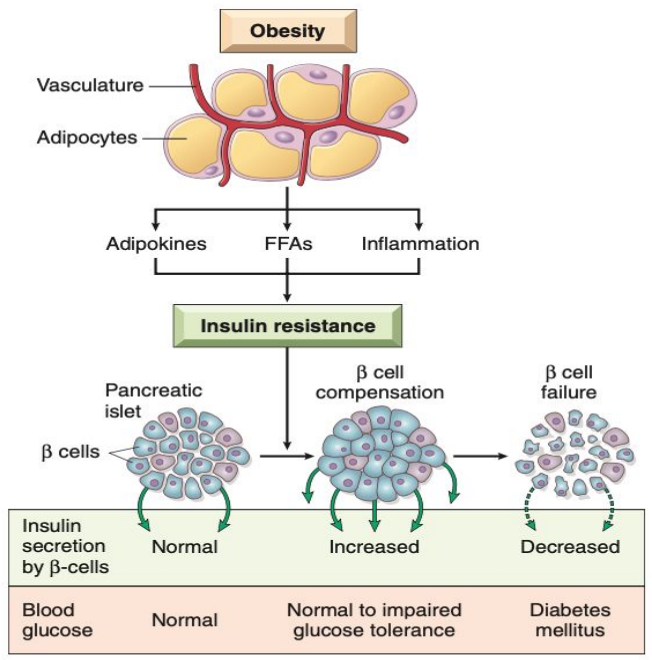


Fig. 20.23 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β cell compensation 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.)*

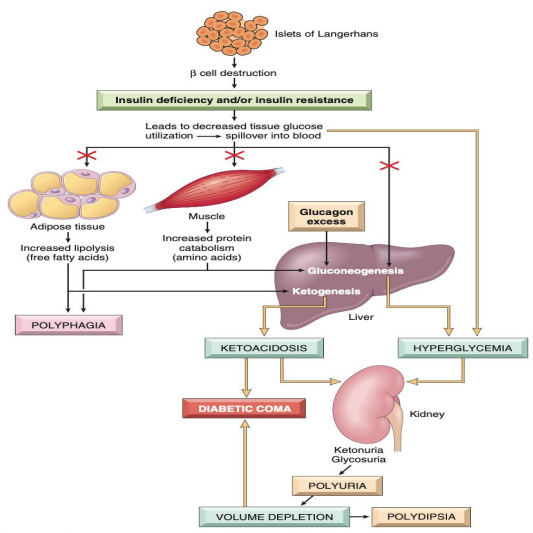


Fig. 20.24 Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus. An absolute insulin deficiency leads to a catabolic state, eventuating in ketoacidosis and severe volume depletion. These derangements bring about sufficient central nervous system compromise to cause coma and, eventually, death if left untreated.

" اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين "

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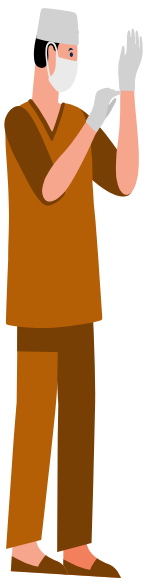

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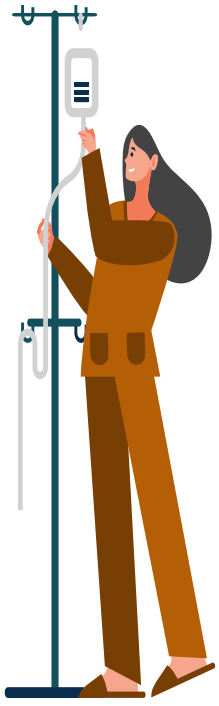

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