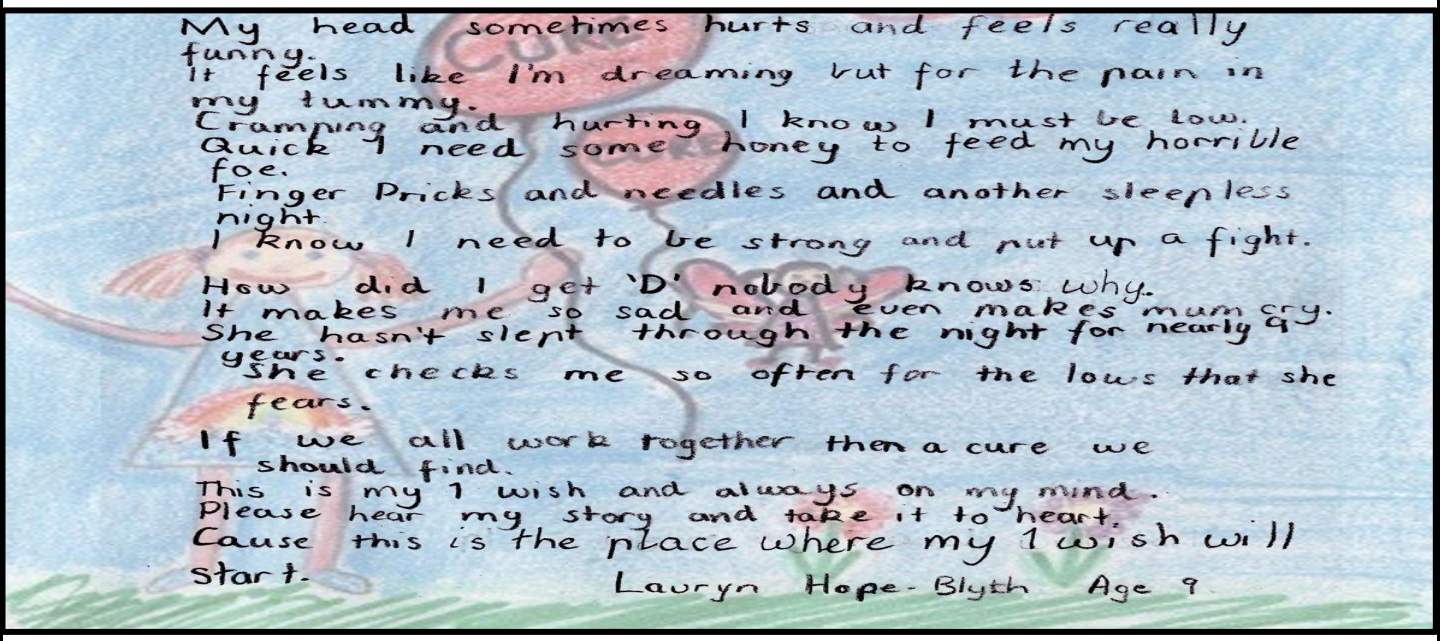
جامعة الملك سعود
King Saud University

PATHOLOGY
TEAM 437

MED437
KING SAUD UNIVERSITY

واعلموا أن مهمتكم ليست ورقة تنالونها.....
إنما مهمتكم أمة تحيونها.....

Diabetes Mellitus



Part of a poem written by a 9 years old child with Type 1 Diabetes
إن أجر هذه المحاضرة لنا في كل مريض خلصتموه يوما من سقمه,ورددتم له عافيته

Revised By
Hadeel Awartani Abdullah AlOmar

الشكر موصول لجميع من عمل على هذه المحاضرة:

القادة: فايز غياث الدرسوني — شيرين العكيلي

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رناد الفرم

Objectives:

- Understand the structure of 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

Color index:
-Text
-important
-Notes
-Extra

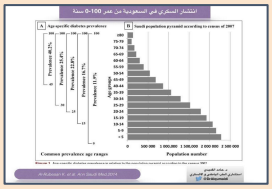
The endocrine pancreas

Islets of Langerhans, contain four major cell types.

PP (pancreatic polypeptide)	δ cells	α cell	β cell
Contains unique pancreatic polypeptide, VIP that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes. Enterochromaffin	contain somatostatin	secretes glucagon increase blood sugar	secretes insulin decrease blood sugar

Diabetes Mellitus (DM)

What is DM?



- 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 (cell resistance/ insulin deficiency), insulin action (insulin-resistant),or most commonly, both.
- Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations in USA.

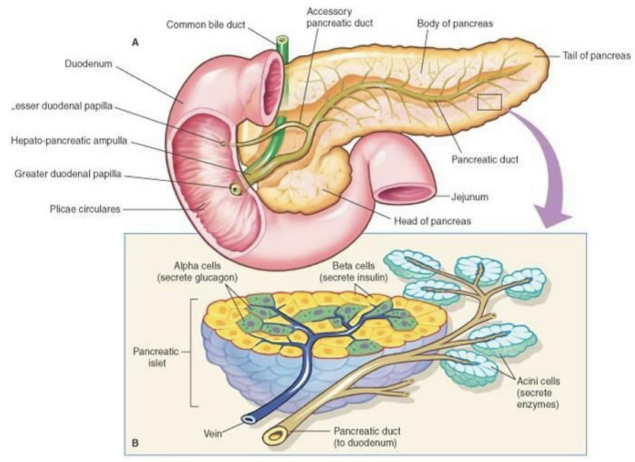


Table 20.5 Simplified Classification of Diabetes

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.

Diagnosis of Diabetes Mellitus (DM)

(Extra): notes for understanding :click !

Normal blood glucose levels 70 to 120 mg/dL, maintained in a very narrow range.
According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diagnostic criteria for diabetes include the following: a lot of times diabetes is asymptomatic

Test one of these is enough	Blood Glucose level indicate DM (1 of 3)
1-random plasma glucose	Greater or equal to 200 mg/dL, with classical signs and symptoms (increasing weight, Polydipsia , polyuria) patient doesn't have to fast
2-fasting plasma glucose	126 mg/dL or more ,on more than one occasion(It is done on more than one occasion to avoid false dx).
3- 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.
4-glycated hemoglobin (HbA1C) level	greater than or equal to 6.5% (glycated hemoglobin is further discussed under chronic complications of diabetes)

- 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.

Prediabetes

Defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes.
People with impaired glucose tolerance (prediabetes) have a significant risk for progression to overt (frank) (Visible) diabetes over time.

Impaired glucose tolerance (prediabetes) is defined as:

1. A fasting plasma glucose between 100 and 125 mg/dL(110-126 in male slides) ("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%

★ 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.patient has to change lifestyle to avoid

★ In addition, individuals with prediabetes have an elevated risk of cardiovascular disease.

Classification Diabetes Mellitus (DM)

Type 1 Diabetes

Is an autoimmune disease characterized by pancreatic β cell destruction and 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.

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. Much more common
very much related to obesity

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.

NOTE: The majority of type 1 is with children but it can come occur in adults and vice versa.

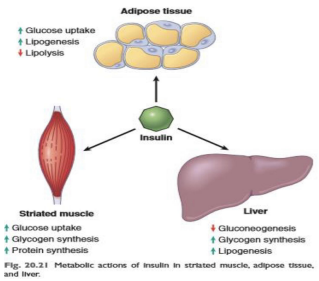


Fig. 20.2.1 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

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% for the symptoms to show less than 90% asymptomatic of the beta cells 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.**

- **Type 2 diabetes is a heterogeneous, prototypical and multifactorial complex disease that involves interactions of**
  - **genetics.**
  - **environmental risk factors (**such as a sedentary lifestyle and dietary habits)
  - **inflammation.**
- **Unlike type 1 diabetes, however, there is no evidence of an autoimmune basis.**
- **recent large-scale genome-wide association studies, have identified more than a dozen susceptibility loci called "diabetogenic" genes.**

- **Autoantibodies** against a variety of beta cell antigens, are detected in the blood of 70% to 80% of patients.
- **Genetic susceptibility**: 90% and 95% of white patients with type 1 diabetes have ***HLA-DR3,* or *DR4. Several non-HLA genes also increase susceptibility to type 1 diabetes.*** *not all who have it have diabetes*
- **Environmental factors,** especially infections, may be involved in type 1 diabetes. because protein part of the virus is similar to that of the beta cells

The two metabolic defects that characterize type 2 diabetes are: *not single gene related*

1. **A decreased ability of peripheral tissues to respond to insulin (<u>insulin resistance</u>).** which in the beginning would be increased insulin secretion then they will have failure to secrete
2. **<u>Beta cell dysfunction</u> that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.**

1-Obesity and Insulin Resistance

*Basically when someone is obese there will be too much fat accumulated within cells that will provide energy making the cell full شبعانه and will not need further energy thus it will stop taking insulin in

- ***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. 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.
- Metabolic syndrome Usually prediabetes 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.

Obesity can adversely impact insulin sensitivity in numerous ways:

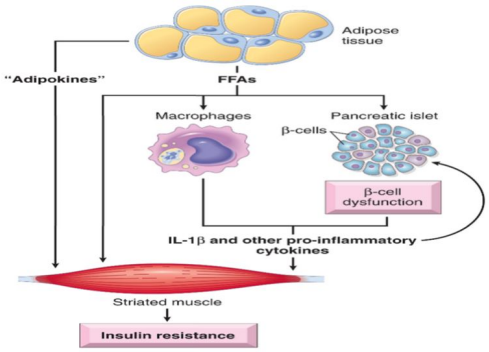
★ **Excess FFAs:** studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity.

★ **Adipokines :**are hormones secreted from adipose tissue,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.

2- 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.



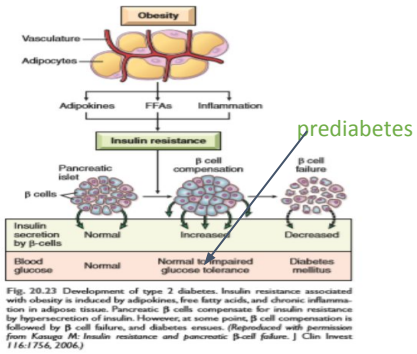


Fig. 20.23 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β cell compensation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

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) and
  - Maturity onset diabetes of the young (MODY), which develops beyond the neonatal period but usually before 25 years of age.
- 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.
- MODY can be the result of inactivating mutations in one of six genes

Gestational diabetes: all pregnant ladies have to be screened

- 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 periconception period) have an increased risk for stillbirth (abortion) 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.
- may continue after parturition in a small proportion of these patients.
- These women highly susceptible to overt T2DM later in life.

Acute Metabolic Complications due to hyperglycemia of Diabetes

- 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.

Acute Metabolic Complications of Diabetes

Diabetic Ketoacidosis (Type 1)

*Why type 1? Because in type one there's so much deficiency of energy that cells require and therefore ketones are produced for energy, in type 2 there's a sufficient amount due to fat accumulation in cells

- In **type 1 diabetes**: any forms of stress may worsen the metabolic imbalance, 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 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***
- In patients with type 1 diabetes, deviations from normal dietary intake, unusual physical activity, infection, or any other forms of stress may rapidly influence the metabolic balance, predisposing the affected person to diabetic ketoacidosis,
- Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness.

Hyperosmolar Non-ketotic Coma (Type 2)

- Also may manifest with polyuria and polydipsia, but unlike in type 1 diabetes, patients often are older than 40 years and frequently are obese.
- Patients with **type 2 diabetes** may develop **hyperosmolar nonketotic coma. 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. Why type 2? It's because insulin resistance creates hyperinsulinemia and hyperglycemia therefore more likely to trigger osmosis and hyperosmolarity of blood

Morphology of DM

Lesions in the pancreas are inconstant "not significant" and rarely of diagnostic value. we don't take pancreas biopsy for diagnosing diabetes, Diagnosis is by biochemical tests.

One or more of the following alterations may be present:

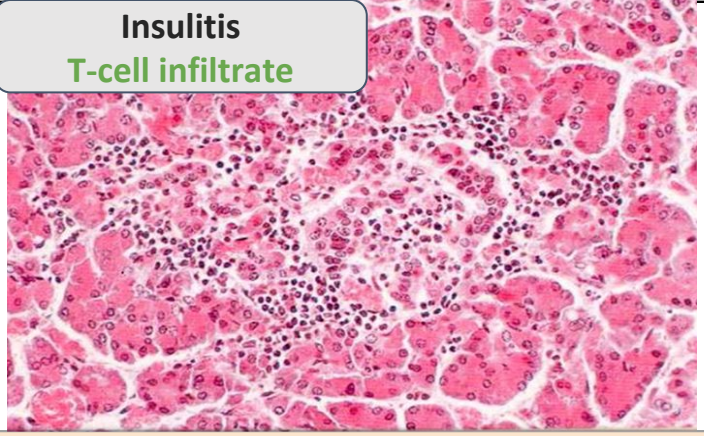
★ **Reduction in the number and size of islets.** This change most often is seen in **type 1 diabetes.**

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

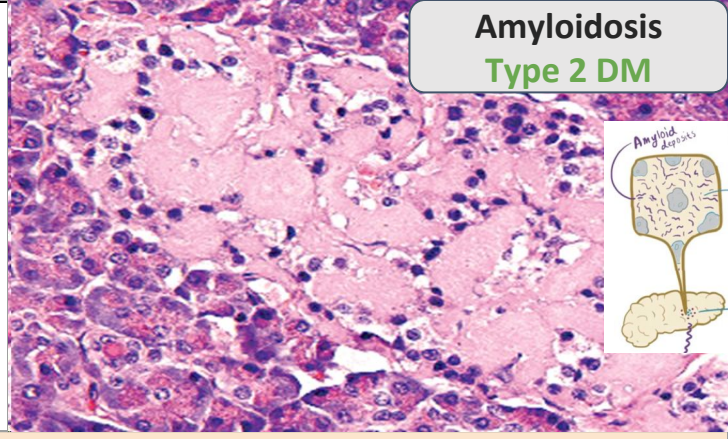
★ **Amyloid replacement of islets in long-standing type 2 diabetes,** appearing as deposition of pink, amorphous material. At advanced stages fibrosis also may be observed.

★ An **increase in the number and size of islets**, especially characteristic of nondiabetic **newborns of diabetic mothers**. If the pregnant woman is diabetic, the fetus will receive excessive amount of blood glucose. The fetus pancreas compensate by producing more insulin.

Insulitis
T-cell infiltrate



Amyloidosis
Type 2 DM



Summary

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

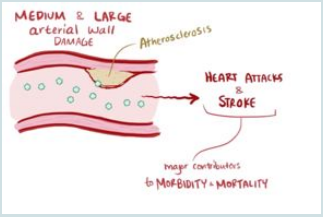
HLA, Human leukocyte antigen; *MHC*, major histocompatibility complex.

Chronic complications 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

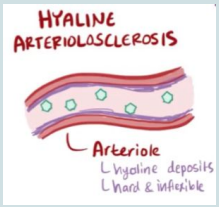
- large- and medium-sized muscular arteries (diabetic macrovascular disease)
- small-vessels (diabetic microvascular disease).

Macrovascular disease



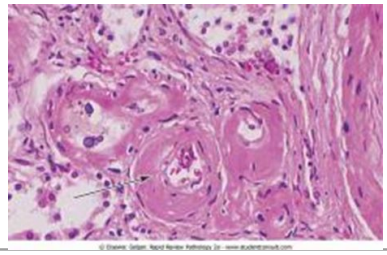
- The hallmark of diabetic macrovascular disease is accelerated **atherosclerosis** affecting the **aorta and large and medium-sized arteries.**
- **Myocardial infarction**, caused by atherosclerosis of the coronary arteries, is the **most common cause of death in diabetics.**
- **Gangrene** of the lower 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



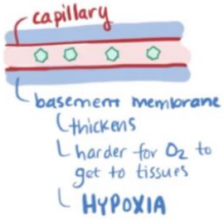
•the vascular lesion **associated with hypertension**, is both more prevalent and **more severe in diabetics** than in non diabetics.

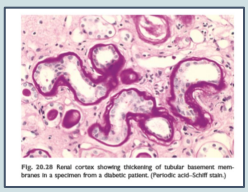
•It takes the form of an amorphous, **hyaline thickening** of the wall of the arterioles, which causes narrowing of the lumen.



Sclerosis = hyaline + fibrosis
Why fibrosis? It could be as result of tissue damage from Glycated end products that cause damage and fibrosis

Microangiopathy



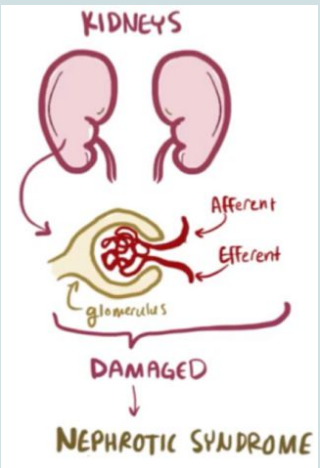


•One of the most consistent morphologic features of diabetes is **diffuse thickening of basement membranes**. The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla.

•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, retinopathy, and some forms of neuropathy.
Recall: Oxygen exchange occurs in capillaries and That glucose can bind to amino acids of proteins "collagen" which is found with within blood vessels making a thick basement membrane and decreased oxygen supply.

Nephropathy



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

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

•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.

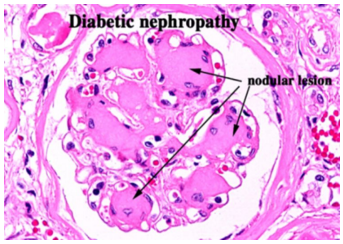
•**Diffuse mesangial sclerosis** consists of a diffuse increase in mesangial **matrix** along with mesangial **cell** . When glomerulosclerosis becomes marked, patients manifest the **nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema.**

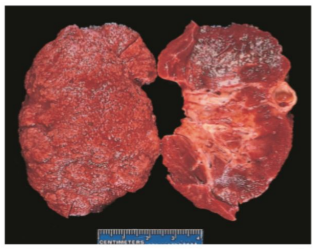
•**Nodular glomerulosclerosis**: ball-like deposits of a laminated matrix situated in the periphery of the glomerulus . These nodules are **PAS-positive** "special stain". This distinctive change has been called the **Kimmelstiel-Wilson lesion "IMPORTANT"**

Nephropathy

•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**

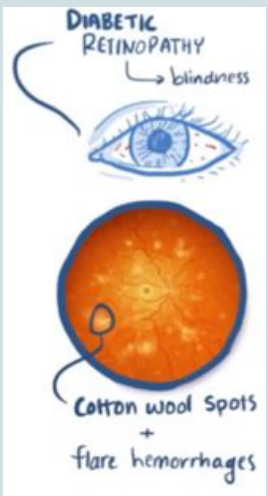




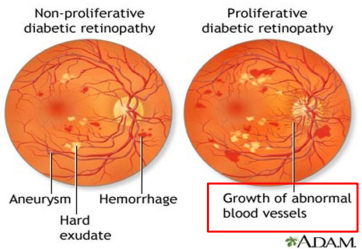
•**Pyelonephritis** is an acute or chronic **inflammation of the kidneys** that usually begins in the interstitial tissue and then spreads to involve the tubules.
Both the acute and chronic forms of this disease occur in non-diabetics as well as in diabetics but **more common in individuals with diabetes**,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

Ocular Complications of Diabetes

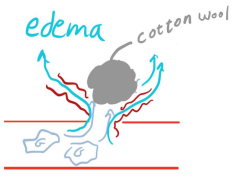


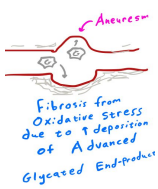
•The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.
•Retinopathy, the most common pattern



•The lesion in the retina takes two forms:-

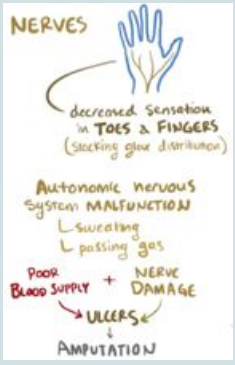
1-nonproliferative (background) retinopathy:
includes **hemorrhages**, **retinal exudates** (cotton wool sots), **microaneurysms**, venous dilations, **edema**, and, most importantly, **thickening** of the retinal capillaries (microangiopathy). The retinal exudates can be "soft" (microinfarcts) or "hard" (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.
Glycated end products can cause damage to
Muscle layer of arteries leading to aneurysm
Or transmural leading to hemorrhages





2-proliferative retinopathy:
is a process of **neovascularization** "new blood vessels formation" **and fibrosis**. This lesion leads to **serious** consequences, including **blindness**, especially if it involves the macula and retinal detachment.

Diabetic Neuropathy.



- The **central and peripheral nervous systems** are not spared by diabetes.
- 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. Since sensation is weak, they have to extra care of their feet.
- Other forms include **autonomic neuropathy**, which produces **disturbances in bowel and bladder function** and diabetic mononeuropathy, which may manifest as sudden foot drop or wrist drop.
- **Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.**

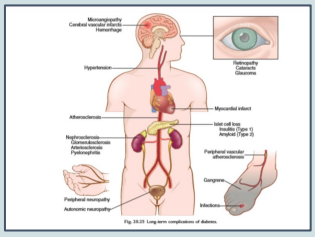
Infection

•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 " simple" **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 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.

Organisms love eating glucose also According to dr.najeeb the wbc May be "drunk" with glucose making them dysfunctional allowing more infections

•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.

Summary: pathoma

Diabetes

I. BASIC PRINCIPLES

A. Composed of clusters of cells termed islets of Langerhans (Fig. 15.11)
B. A single islet consists of multiple cell types, each producing one type of hormone.
C. Insulin is secreted by beta cells, which lie in the center of the islets.
1. Major anabolic hormone; upregulates insulin-dependent glucose transporter
protein (GLUT4} on skeletal muscle and adipose tissue (glucose uptake by GLUT4 decreases serum glucose)
2. Increased glucose uptake by tissues leads to increased glycogen synthesis, protein synthesis, and lipogenesis.
D. Glucagon is secreted by alpha cells; it opposes insulin in order to increase blood glucose levels (e.g., in states of fasting) via glycogenolysis and lipolysis.

II. TYPE I DIABETES MELLITUS

A. Insulin deficiency leading to a metabolic disorder characterized by hyperglycemia
B. Due to autoimmune destruction of beta cells by T lymphocytes
1. Characterized by inflammation of islets 2. Associated with HLA-DR3 and HLA-DR4 3. Autoantibodies against insulin are often present (sign of damage) and may be seen years before clinical disease develops.
C. 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 muscle.

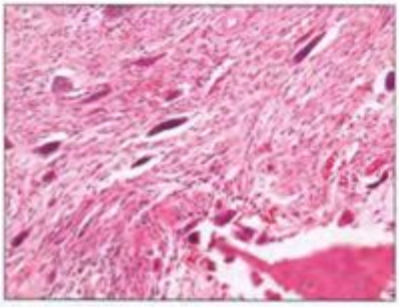


Fig. 15.10 Osteitis fibrosa cystica.

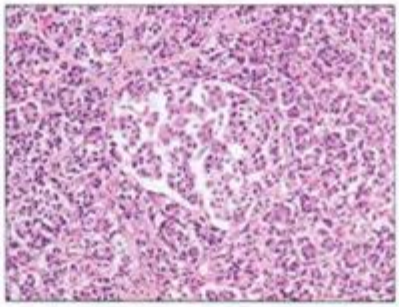


Fig. 15.11 Islets of Langerhans.

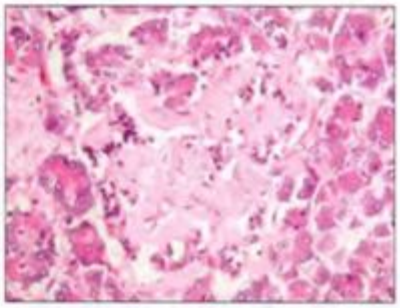


Fig. 15.12 Amyloid in islets, type II DM.

2. Weight loss, low muscle mass, and polyphagia-Unopposed glucagon leads to gluconeogenesis, glycogenolysis and lipolysis, which further exacerbates
hyperglycemia.
3. Polyuria, polydipsia, and glycosuria-Hyperglycemia exceeds renal ability to reabsorb glucose; excess filtered glucose leads to osmotic diuresis.
4. Treatment involves lifelong insulin.
D. Risk for diabetic ketoacidosis
1. Characterized by excessive serum ketones
2. Often arises with stress (e.g., infection); epinephrine ne stimulates glucagon secretion increasing lipolysis (along with gluconeogenesis and glycogenolysis).
i. Increased lipolysis leads to increased free fatty acids (FFAs).
ii. Liver converts FFAs to ketone bodies (p -hydroxybutyric acid and acetoacetic acid).
3. Results in hyperglycemia(> 300 mg/dL), anion gap metabolic acidosis, and hyperkalemia 4. Presents with Kussmaul respirations, dehydration, nausea, vomiting, mental
status changes, and fruity smelling breath (due to acetone)
5. Treatment is fluids (corrects dehydration from polyuria), insulin, and replacement of electrolytes (e.g., potassium).

Summary: pathoma

III. TYPE 2 DIABETES MELLITUS

A. End-organ insulin resistance leading to a metabolic disorder characterized by hyperglycemia 1. Most common type of diabetes (90% of cases); affects 5 - 10% of the US population 2. Incidence is rising.
B. Arises in middle-aged, obese adults
1. Obesity leads to decreased numbers of insulin receptors.
2. Strong genetic predisposition exists.
C. Insulin levels are increased early in disease, but later, insulin deficiency develops due to beta cell exhaustion; histology reveals amyloid deposition in the islets (Fig. 15.12). D. Clinical features include polyuria, polydipsia, and hyperglycemia, but disease is often clinically silent.
E. Diagnosis is made by measuring glucose levels {normal is 70-120 mg/dL).
1. Random glucose > 200 mg/dL
2. Fasting glucose> 126 mg/dL
3. Glucose tolerance test with a serum glucose level > 200 mg/dL two hours after glucose loading
F. Treatment involves weight loss (diet and exercise) initially; may require drug therapy to counter insulin resistance (e.g., sulfonylureas or metformin) or exogenous insulin after exhaustion of beta cells G. Risk for hyperosmolar non-ketotic coma
I. High glucose(> 500 mg/dL) leads to life-threatening diuresis with hypotension and coma. 2. Ketones are absent due to small amounts of circulating insulin.

IV. LONG-TERM CONSEQUENCES OF DIABETES

A. Nonenzymatic glycosylation (NEG) of vascular basement membranes
1. NEG of large- and medium-sized vessels leads to atherosclerosis and its resultant complications.
i. Cardiovascular disease is the leading cause of death among diabetics.
ii. Peripheral vascular disease in diabetics is the leading cause of non traumatic amputations.
2. EG of small vessels (arterioles) leads to hyaline arteriolosclerosis (Fig. 15.13A).
i. Involvement of renal arterioles leads to glomerulosclerosis, resulting in small, scarred kidneys with a granular surface (Fig. 15.13B).
ii. Preferential involvement of efferent arterioles leads to glomerular hyperfiltration injury with microalbuminuria that eventually progresses to nephrotic syndrome; characterized by Kimmelstiel-Wilson nodules in glomeruli
3. NEG of hemoglobin produces glycated hemoglobin (HbA1c), a marker of glycemic control.
B. Osmotic damage
I. Glucose freely enters into Schwann cells (which myelinate peripheral nerves), pericytes of retinal blood vessels, and the lens.
2. Aldose reductase converts glucose to sorbitol, resulting in osmotic damage.
3. Leads to peripheral neuropathy, impotence, blindness, and cataracts; diabetes is the leading cause of blindness in the developed world.

V. PANCREATIC ENDOCRINE NEOPLASMS

A. Tumors of islet cells; account for< 5% of pancreatic neoplasms.
I. Often a component of MEN 1 along with parathyroid hyperplasia and pituitary adenomas
B. Insulinomas present as episodic hypoglycemia with mental status changes that are relieved by administration of glucose.
I. Diagnosed by decreased serum glucose levels (usually< 50 mg/dL), increased insulin, and increased C-peptide
C. Gastrinomas present as treatment-resistant peptic ulcers (Zollinger-Ellison syndrome); ulcers may be multiple and can extend into the jejunum.
D. Somatostatinomas present as achlorhydria (due to inhibition of gastrin) and cholelithiasis with steatorrhea (due to inhibition of cholecystokinin).
E. VI Po mas secrete excessive vasoactive intestinal peptide leading to watery diarrhea, hypokalemia, and achlorhydria.

Questions

Q1) A male patient with Type one diabetes have balance problems in the dark and decreasing in his visual acuity. What's the most probable cause?
A. Neuropathy
B. Retinopathy
C. Infection
D. deep vein thrombosis

Q2) A study done to a large group of diabetic patients, a portion of these patients have HLA-DR3 and HLA-DR4 alleles. What is the pancreatic changes in this portion of patients?
A. Amyloid deposition within and around the islets
B. Islets chronic inflammation
C. Normal islets surrounded by fibrous stroma
D. Fibrosis of acini and Neutrophil deposition in islets

Q3) Which of the following is a common and recognized renal complication of diabetes mellitus?
A. Nodular glomerulosclerosis
B. Nodular glomerulonephritis
C. Armani-Epstein
D. Renal papillary necrosis

Q4) Which of following is an acceptable etiology of type 2 diabetes?
A. Islet autoimmunity
B. Insulin resistance
C. Mitochondrial DNA gene mutation
D. Viral infection

Q5) Which one of the following is an eye complication of long standing diabetes mellitus?
A. Conjunctivitis
B. Scleritis
C. Glaucoma
D. Optic nerve glioma

Q6) A 63 years old diabetic male presented to his local doctor due to intermittent leg pain, which was relieved by resting. Negative dorsalis pedis. Which of the following could be the the cause of this complication?
A. Autoimmune vasculitis
B. Deep vein thrombosis
C. Atherosclerosis
D. Neuropathy

Q7) A 59-year old female who has diabetes mellitus for more than 25 years. Recently she began to complain of decreasing visual acuity. She has no eye pain and her intraocular pressure is normal. Which of the following lesion could be the possible cause?
A. Cytomegalovirus retinitis
B. Proliferative retinopathy
C. Glaucoma
D. Conjunctivitis

Q8) Which ONE of the following histopathologic features is most likely to be seen in a biopsy taken from type II diabetic patient?
A. Lymphocytes infiltrating the Langerhans
B. Amyloid depositions
C. Scattered reactive inflammatory cells as neutrophils
D. Diffuse destruction of beta cells

Q9) What are the genes involved in developing diabetes type 1?
A. HLA-DR3.
b. HLA-DR5.
c. HLA-DR7.

Q10) What is primary cause of diabetic complication including retinopathy , nephropathy and peripheral neuropathy?
A. Low immunity
B. Microangiopathy
C. Atheroma
D. Systemic disturbances

Q11) What is the most frequent pattern of involvement in neuropathy?
A. Peripheral symmetric neuropathy
B. Peripheral asymmetric neuropathy
C. Mononeuropathy
D. Autonomic neuropathy

Q12) an 18 year-old male, previously healthy, came to the general practitioner with 1 month history of polydipsia and polyuria. No long-term medications are used. Random blood glucose concentration is 300 mg/dL. What is the most likely diagnosis(what is the answer if you did know that the disease caused by a single gene mutation)?
A. Type 1 DM
B. Type 2 DM
C. Maturity-onset Diabetes of the Young (MODY)

Q13) For patient in the previous Q ,what is the most likely genetic mutation he will have?
a) RAS
b) MEN2
c) Hepatocyte Nuclear Factor 1α gene

Q14) Which of the following is right in DM?
a) Single disease due to hyperglycemia
b) Delta cells are hypofunctioning.
c) Caused by decrease in insulin action
d) The patient could develop hypotension

1-a
2-b
3-a
4-b
5-c
6-c
7-b
8-b
9-a
10-b
11-a
12-c
13-c
14-c

واعلموا أن مهمتكم ليست ورقة تنالونها.....
إنما مهمتكم أمة تحيونها.....

(وما العلم إلا شُعلةٌ ننير به الظلمة)

بدأنا هذه الوحدة (وحدة الغدد الصماء) بعبارة "واعلموا انه مهمتكم ليست ورقة تنالونها إنما مهمتكم أمة تحيونها" علمنا هو حجتنا، نرفع به الجهل عن أنفسنا، لغاية سمية وهي التعرف اكثر على عالمنا (جسدنا) ففي هذا الوحدة تعلمنا الكثير عن الأمراض التي يمكن ان تصيب الغدد الصماء ونرى ان الكثير منها منتشر حولنا فوظيفتنا بعد معرفة العلة معرفة العلاج، فالأفضل قادم بإذن الله وببذلنا جهدنا على تحسين أنفسنا قائم فما الأمة الا أنا وأنت وهم وهن فإذا لم يصلح كل منّا نفسه لم يكن للامة صلاح، اخلصوا دراستكم واحتسبوا الأجر فنحن نرى فيكم الأمل العظيم مستقبلا.

ولأعضاء الفريق: مررتم بالكثير معنا، وبذلتم ما تستطيعون فالشكر لا يجزيكم حقكم رفع الله قدركم وزاد علمكم، شكرا من الأعماق للجميع.

نعتذر عن أي تقصير بدر منا والى اللقاء إلى الوحدة القادمة بإذن الله نراكم قريباً...

القادة: فايز غياث الدرسوني — شيرين العكيلي

الأعضاء:

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