Lecture 4 & 5
Diabetes

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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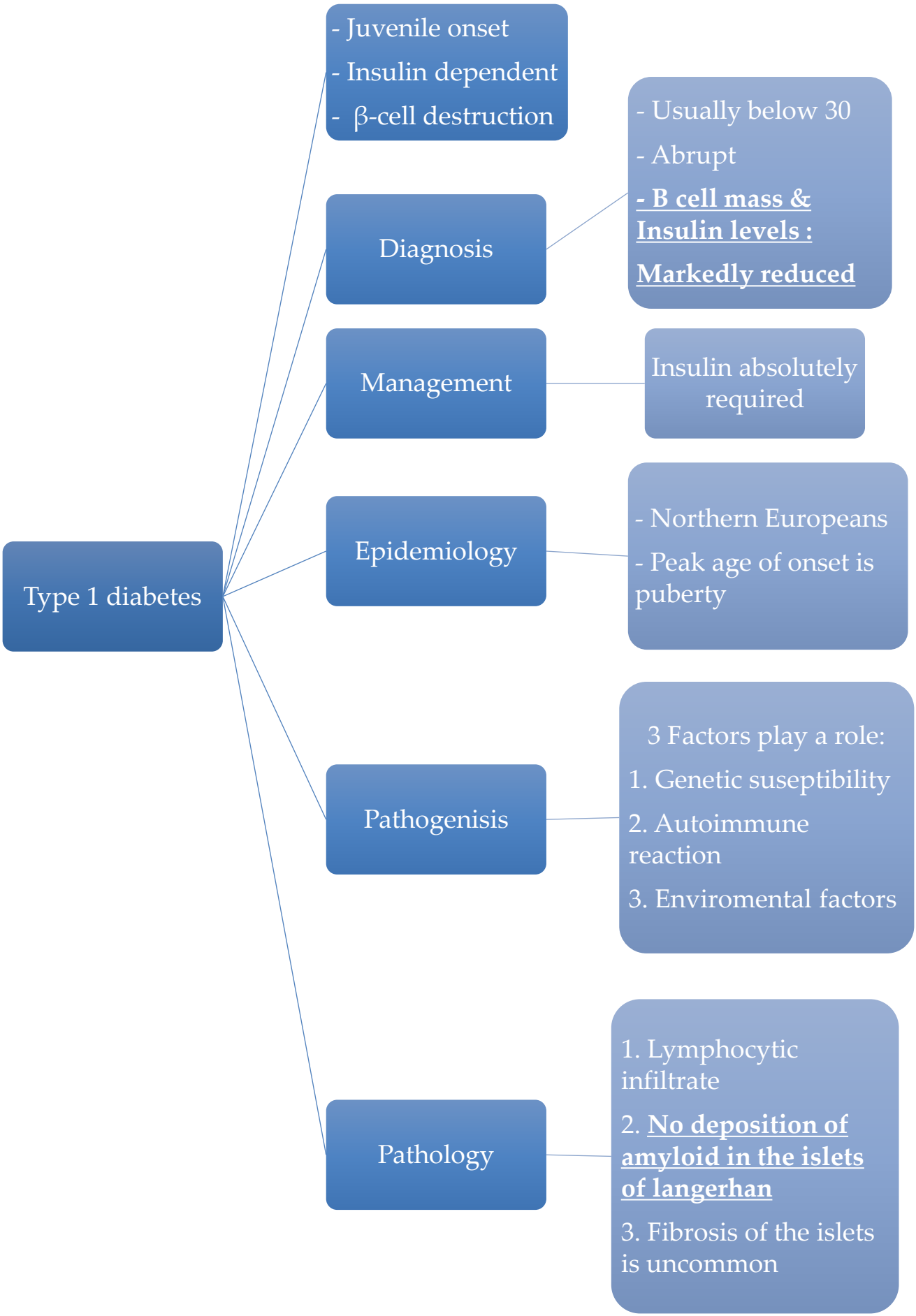
Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

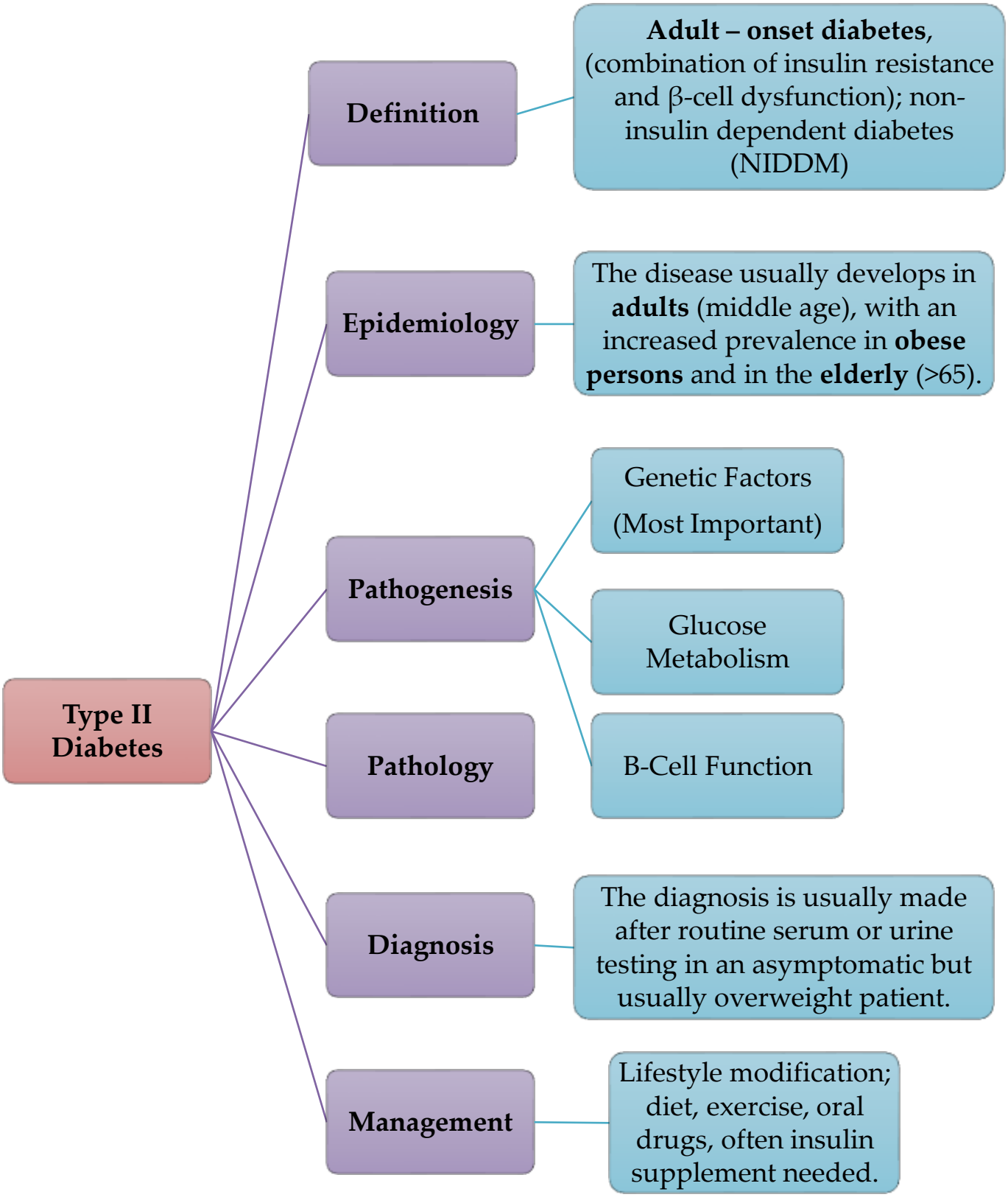
Objectives:

- Understand the structure of the pancreas and have a basic understanding of its function
- Know the various hormones secreted by the pancreas
- Have an understanding of the classification, pathogenesis, clinical features and complications of diabetes mellitus and have a basic knowledge of the theories of its pathogenesis.
- The student should have an understanding of 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.

References: Dr. Rikabi & Dr. Hala's notes, Lecture Slides & Robbins.

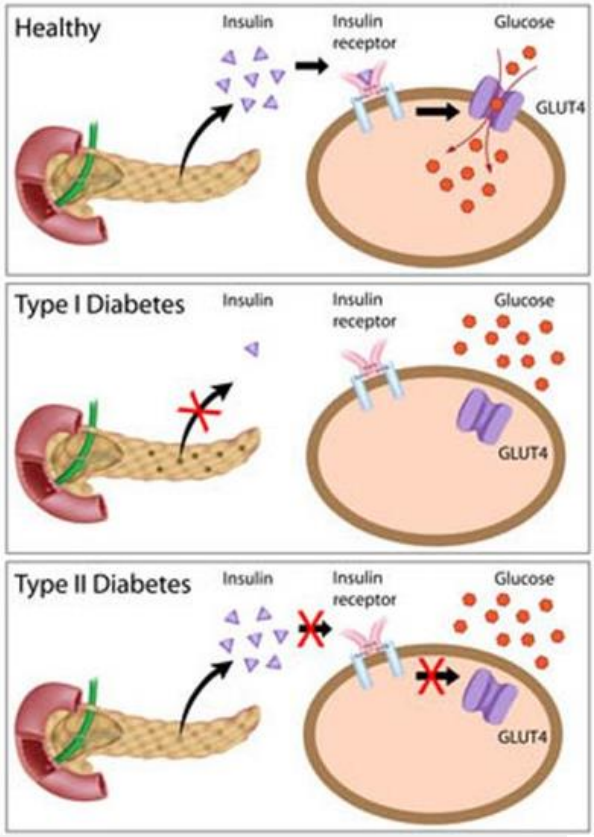
**** The Two lectures are only 10 pages; the rest are summaries & MCQs****


Type 1 diabetes
- Juvenile onset
- Insulin dependent
- β-cell destruction
Diagnosis
- Usually below 30
- Abrupt
- B cell mass & Insulin levels :
Markedly reduced
Management
Insulin absolutely required
Epidemiology
- Northern Europeans
- Peak age of onset is puberty
Pathogenisis
3 Factors play a role:
1. Genetic suseptibility
2. Autoimmune reaction
3. Enviromental factors
Pathology
1. Lymphocytic infiltrate
2. No deposition of amyloid in the islets of langerhan
3. Fibrosis of the islets is uncommon


Type II Diabetes
Definition
Adult – onset diabetes, (combination of insulin resistance and β-cell dysfunction); non-insulin dependent diabetes (NIDDM)
Epidemiology
The disease usually develops in adults (middle age), with an increased prevalence in obese persons and in the elderly (>65).
Pathogenesis
Genetic Factors (Most Important)
Glucose Metabolism
B-Cell Function
Pathology
Diagnosis
The diagnosis is usually made after routine serum or urine testing in an asymptomatic but usually overweight patient.
Management
Lifestyle modification; diet, exercise, oral drugs, often insulin supplement needed.

We recommend you watch this video before starting the lecture.

T2DM vs T1DM



Structure and Function of Endocrine Pancreas.

The pancreas consists of two separate functional units, the exocrine pancreas, which secretes digestive enzymes in the duodenum and the endocrine pancreas which secretes a number of different hormones. The endocrine pancreas consists of – 1 million islets of Langerhans, which are scattered throughout the gland.

Insulin and **glucagon** are the hormone responsible for maintaining blood sugar levels; insulin exerts a hypoglycemic effect and glucagon exerts a hyperglycemic effect. The two main disorders of the islet cells are diabetes mellitus and islet cell tumors.

What's the difference between plasma and serum? Plasma is derived from the blood, if it was preserved it will be named so, if it wasn't preserved a clot will form and the fluid above will be named serum.

You must shake the blood gently to measure it, why? If you shake it vigorously, you rupture then RBCs, so you're allowing the K+ electrolytes to escape into the plasma, hence you will find it VERY high. 7.3 for example, that should mean he's dead.

Each islet is composed of a cluster of a number of different cell types, each cell type synthesizing and secreting a different hormone:

Cell type	**Hormone synthesized**	**Action**
β (beta)	Insulin	▪ ↑ glucose entry into cells, glycogen synthesis and prevents breakdown. ↓ lipolysis
α (alpha)	Glucagon	▪ ↑ glycogen breakdown & gluconeogenesis
δ (delta)	Somatostatin	↓ secretion of insulin and glucagon
PP	PP	Exerts a number of gastrointestinal effects
Enterochromaffin	VIP[1]	Stimulates intestinal fluid secretion
D1	Serotonin	▪ Potent vasodilator & ↑ intestinal motility

Glucose Metabolism

- Normally, the extracellular concentration of is maintained in a tightly limited range by the opposing actions of insulin and glucagon.
- After a carbohydrate-rich meal, absorption of glucose from the gut leads to an ↑ in blood glucose, which ↑ insulin secretion by the pancreatic B-cells and the consequent insulin-mediated ↑ in glucose uptake by skeletal muscle and adipose tissue.
- At the same time, insulin suppresses hepatic glucose production.

[1] Vasoactive intestinal polypeptide

Diabetes Mellitus:

Runs in families (not always), increasing in prevalence. Defined clinically as either a fasting plasma glucose level ≥ 7.1mmol/L (140 mg/dL) or 2-hours postprandial glucose ≥ 11mmol/L (200mg/dL).

A condition characterized by an **absolute or relative deficiency of insulin** and/or **insulin resistance**, inducing **hyperglycemia**.

- A major health problem that is the leading cause of **end-stage renal disease**, **adult-onset blindness**, and **non-traumatic lower extremity amputations**.

Classification: There are two main types of Diabetes Mellitus (T1 & T2), we also have 3 primary causes of diabetes, the rest are secondary:

T1DM	Juvenile-onset diabetes; **insulin dependent diabetes**, 10% of all cases.
T2DM	Adult – onset diabetes, combination of peripheral insulin resistance and β-cell dysfunction, non-insulin dependent diabetes (NIDDM), which accounts for 80 – 90% of all cases.
T3-MODY	Maturity onset diabetes of the **young** (MODY) is a rare case of DM, autosomal dominant. Due to a **genetic defect in β cell function** and is rather common in Gulf and Arabian countries.

In KSA: T2 & MODY are commoner. Genetic predisposition: Little in type1, Strong in type 2 & Very strong in MODY. There are different types depending on the affected gene. Manifestation of type 1 but appear as type 2, so absolute deficiency of insulin appears in adult.

Other Causes of Diabetes (secondary):

Defects	**Genetic**	In insulin action: Type A insulin resistance, Lipoatrophic diabetes, including mutations in *PPARG*
	Exocrine pancreatic	**Acute** or chronic pancreatitis, Neoplasia, Cystic fibrosis…
Infections		CMV, Coxsackie B virus, Congenital rubella
Drugs		Glucocorticoids, Thyroid hormone, Interferon-α, **β-adrenergic agonists**
Genetic syndromes		Associated with DM: Down's, Kleinfelter syndrome, Turner syndrome, Prader-Willi syndrome and **acromegaly**
Gestational diabetes mellitus (rare)		

Diagnosis of DM: Any one of three criteria:

1- A random glucose concentration > 200 mg/dL, with classical signs and symptoms.
2- A fasting glucose concentration ≥ 126 mg/dL on more than one occasion.
3- An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is greater than 200 mg/dL 2 hours after a standard carbohydrate load.
   - Pre-diabetic individuals have a significant risk of progressing to overt diabetes over time, with as many as 5%-10% advancing to diabetes mellitus per year. In addition, **pre-diabetics are at risk for cardiovascular disease.**
   - Those with fasting glucose concentrations greater than 100 mg/dL but less than 126 mg/dL, or OGTT values greater than 140 mg/dL but less than 200 mg/dL, are considered to have impaired glucose tolerance, also known as "pre-diabetes ".

Gold standard for diagnosing DM: Blood glucose (T1) & HbA1c (T2). Why HbA1c? A very high glucose level in the blood → glucose wants to leave but can't enter the cells because of the lack of insulin → starts to attach to Hg in RBCs (irreversible for the following 3 months) → formation of HgA1c → attaches to renal tubules in kidney & cornea leading to various complications.

- In type II, measure HbA_{1c} to know whether DM is under control or not. (+ glucose)
- In a prediabetic, monitor by measuring HbA_{1c}. It ought to be < 42 mmol/mol (<6%)
- In uncontrolled DM, it may exceed 86 mmol/mol(10%)
- Hemolytic anaemia, sickle cell disease and chronic renal/liver diseases **may affect** HbA_{1c} values.

Management:

The most important management is monitoring

- Type 1: **Insulin absolutely required**.
- Type 2: lifestyle modification; diet, exercise, oral drugs, often insulin supplement needed.

Type 1 diabetes:

They believe that the trigger factor is viral infection, because the virus has the same antigen of the beta cells.

An autoimmune disease in which islet destruction (β-cell) is caused primarily by immune effector cells reacting against endogenous beta cell antigens.

- Most commonly develops in childhood, manifests at puberty, and progresses with age.
- Most patients depend on exogenous insulin for survival; without insulin, they develop serious metabolic complications such **as ketoacidosis and coma**.
- **Abrupt** onset, resulting from a chronic autoimmune attack on beta cells (destruction) that usually starts many years before the disease becomes evident.
- The classic manifestations of the disease **(hyperglycemia and ketosis)** occur late in its course, after more than 90% of the beta cells have been destroyed.
- The fundamental immune abnormality is a **failure of self-tolerance inT cells** (how?[2]).
- **The disease is characterized by:**
  - Few if any functional B cells in the islets of Langerhans.
  - Extremely limited or nonexistent insulin secretion.

As a result Body fat rather than glucose is preferentially metabolized as a source of energy.

In turn Oxidation of fat overproduces ketone bodies (acetoacetic acid and B-hydroxybutyric acid)

which are Released into the blood from the liver and lead to metabolic ketoacidosis

Hyperglycemia Results from unsuppressed hepatic glucose out-put and reduced glucose disposal in skeletal muscle and adipose tissue

Hyperglycemia Leads to glucosuria and dehydration from loss of body water into the urine.

If uncorrected The progressive acidosis and dehydration ultimately lead to coma and death

Epidemiology:

- **Most common** among northern Europeans and their descendants and is not seen as frequently among Asians, African-Americans, or Native Americans.
- Can develop at any age, the peak age of onset coincides with **puberty**.
- ↑ incidence in late fall and early winter has been documented in many geographical areas.

Sometimes presents with coma after infection.

Pathogenesis: Separate but inter-related mechanisms have a role in the destructive process:

• Genetic susceptibility • Autoimmune reaction • Environmental event/factors (EF)

[2] A result of some combination of defective clonal deletion of self-reactive T cells in the thymus, defects in the functions of regulatory T cells or resistance of effector T cells to suppression by regulatory cells. Thus, autoreactive T cells not only survive but are poised to respond to self-antigens.

It has been postulated that genetic susceptibility predisposes certain individuals to the development of an autoimmune reaction against the β cells of the islets, and that this autoimmune reaction is triggered by an environmental event (e.g. viral infection, exposure to chemical toxins).

Genetic Factors

- Multiple genetic susceptibility loci, the most important is the **HLA locus on chromosome 6p21 (HLA-D)**. 90-95% of Caucasians with this disease have either a **HLA-DR3 or HLA-DR4 haplotype.** Sometimes HLA-DQ
- 40-50% of T1 diabetics are combined **DR3/DR4 heterozygotes**.
- Several ***non-HLA genes*** also confer susceptibility to T1D, e.g. polymorphisms within the gene encoding insulin, ***CTLA4* and *PTPN22*.** (Explanation[3])
- Fewer than 20% of those with T1DM have a parent or sibling with the disease.
- The children of fathers with T1DM are 3 times more likely to develop the disease than are children of diabetic mothers. **Monozygotic twins**: 50% concordant.

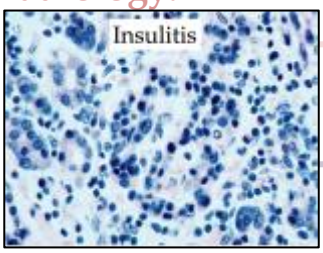
EF

- Viruses and chemicals, CMV, Mumps, group B Coxsackie & Rubella viruses.
  Why? because some viral antigens are antigenically similar to beta cell antigens (molecular mimicry), leading to bystander damage to the islets.
- Geographical and seasonal differences are important in the incidence of T1DM.

Autoimmunity

- Many develop islet cell antibodies against components of the B cells (including insulin itself) months or years before insulin production decreases and clinical symptoms appear, hence, it's found in most newly diagnosed children with DM
- Cell-mediated immune mechanisms, eg. CD8+T lymphocytes pre-dominate and some CD4+cells are also present.
- The infiltrating inflammatory cells also elaborate cytokines, for example, IL-1, IL-6, interferon-alpha, and nitric oxide, which may further contribute to B cell injury.
- Detection of serum antibodies and certain islet antigens remains a useful clinical tool for differentiating between type 1 and type 2 diabetes

Pathology:



Lymphocytic infiltrate in the islets (**insulitis**), sometimes accompanied by a few **macrophages** and neutrophils.

No deposition of amyloid in the islets, unlike T2DM. **No** fibrosis in islets

- As the disease becomes chronic, the B cells of the islets are progressively **depleted of Beta cells.**
- The exocrine pancreas in chronic T1DM often exhibits **diffuse interlobular** and **interacinar fibrosis**, accompanied by **atrophy** of the acinar cells.
- Patients who die shortly after the onset of the disease often exhibit an infiltrate of mononuclear cells in and around the islets of Langerhans, termed insulitis.

Beta cells will be destroyed. That's why they need insulin injections and not hypoglycaemics (hypoglycaemics help cells take up insulin)

[3] CTLA-4 is an inhibitory receptor of T cells and PTPN-22 is a protein tyrosine phosphatase; so, polymorphisms that interfere with their functional activity are expected to set the stage for excessive T cell activation. Polymorphisms in the insulin gene ↓ expression of this protein in the thymus, thus ↓ the elimination of T cells reactive with this self-protein.

Type II diabetes:

Results from a complex interrelationship between **resistance** to the metabolic action of insulin in its target tissues and **inadequate compensatory secretion** of insulin from the pancreas (**β-cell dysfunction**) **"relative insulin deficiency"**.

Epidemiology:

- The disease usually develops in adults (middle age), with an increased prevalence in **obese persons** and in the elderly (>65).
- Recently, T2DM has been appearing in increasing numbers in younger adults and adolescents, owing to **worsening** obesity and lack of exercise in this age group.
- **Heterogeneous disorder** characterized by a combination of **reduced** tissue sensitivity to insulin and **inadequate** secretion of insulin from the pancreas.
- Hyperglycemia in T2DM is a failure of the **B-cells** to meet an **increased** demand for **insulin** in the body.

The number of receptors are reduced and the secretion is normal or increased. T2D is a combination between insulin deficiency & insulin resistance.

Pathogenesis:

The precise mechanisms are unknown, but obesity and genetic factors are important.

Two metabolic mechanisms have been postulated:

- Insulin resistance: A decreased ability of peripheral tissues to respond to insulin.
- Beta cell dysfunction (inadequate insulin secretion in the face of insulin resistance and hyperglycemia).

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

Genetic Factors

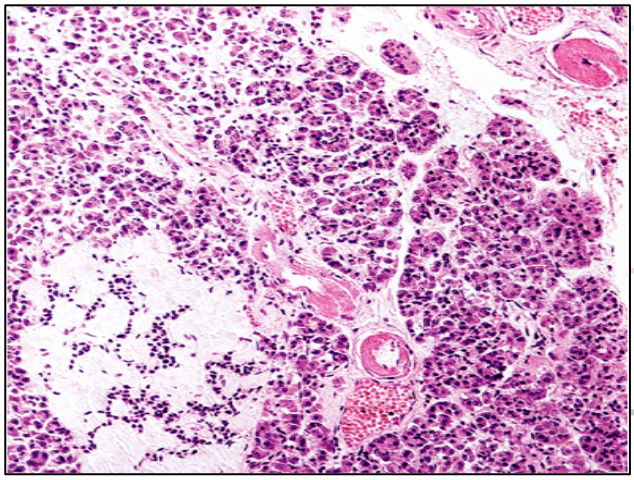
- Multi-factorial, 60% of patients have either a parent or a sibling with the disease. Among monozygotic twins, **both** are almost always affected.
- No association with genes of (MHC). However, some "diabetogenic" genes (susceptibility loci) have been identified. The inheritance pattern is complex and thought to be due to multiple interacting susceptibility genes.
- Constitutional factors such as **obesity** (which itself has strong genetic determinants), **hypertension**, and the **amount of exercise** influence the phenotypic expression of the disorder

B-Cell Function

- Persons with T2DM exhibit impaired B-cell insulin release in response to glucose stimulation. T2D pathogenicity: first amyloidosis and then fibrosis.
- This functional abnormality is specific for **glucose**, since the B-cells retain the ability to respond to other stimulants, such as amino acids.
- May be affected by the chronically ↑ plasma levels of **FFA** in obese persons.

At the beginning beta-cells will compensate and increase the release of insulin, then it will fail and cause glucose intolerance, and diabetes at the end stage.

Pathology:



No consistent reduction in the number or morphologic lesions of **B- cells.** Leukocytic infiltration of the islets (lymphocytes and macrophages).

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

Islet amyloid is often present particularly in patients over 60 years of age (long-standing).

Of note, **both types** may demonstrate islet inflammation early in the disease, although it is typically **more severe** in T1D. In both types inflammation is often absent by the time the disease is **clinically evident**. **Note:** An ↑ in the number and size of islets, especially characteristic of nondiabetic newborns of diabetic mothers. Fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

-Amyloid at the center.
-Amyloid appears red if it is stained by Congo red.

More explanation on pathogenesis

Insulin Resistance:

Defined as the failure of target tissues to respond normally to insulin. Predates the development of hyperglycemia and usually is accompanied by compensatory beta cell hyperfunction and hyperinsulinemia in the early stages of the evolution of diabetes. It leads to:

- ↓ uptake of glucose in muscle & glycolysis.
- Fatty acid oxidation in the liver.
- Inability to suppress hepatic gluconeogenesis.
- Few factors play as important a role in the development of insulin resistance as obesity

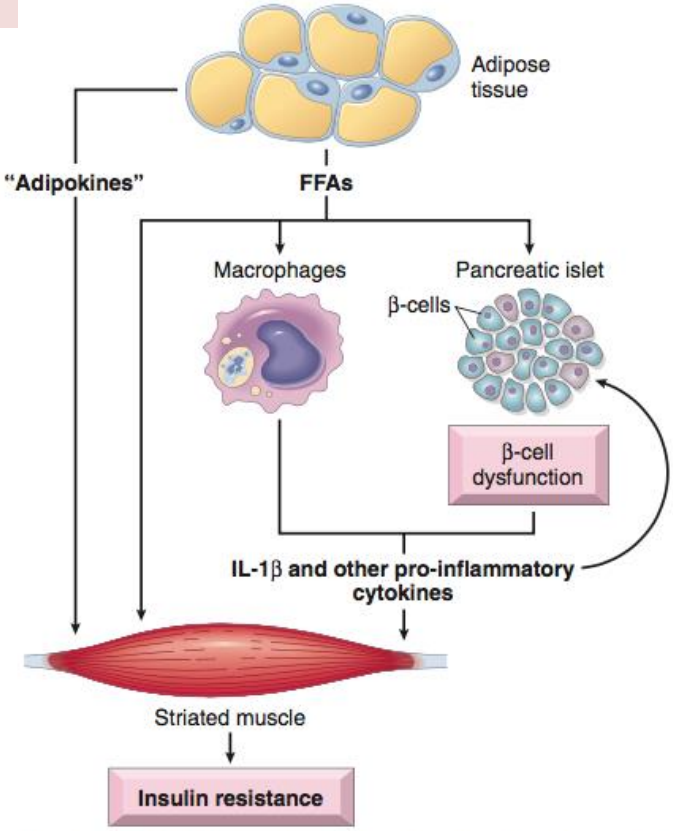


Figure 19–24 Mechanisms of beta cell dysfunction and insulin resistance in type 2 diabetes. Free fatty acids directly cause beta cell dysfunction and induce insulin resistance in target tissues (such as striated muscle, *shown here*), and also induce the secretion of pro-inflammatory cytokines that cause more beta cell dysfunction and insulin resistance.

- Insulin is an anabolic hormone.
How does the obesity lead to diabetes?
FFA can be directly toxic to the beta-cells, or indirectly by inducing the inflammation, both mechanisms will lead to inflammatory response or beta-cell dysfunction, at the end will lead to insulin resistance.

Clinical Features: (Helpful extra explanation)

T1DM

Related to ↑ gluconeogenesis and hyperglycaemia resulting from a lack of insulin. In the initial 1-2yrs of manifestation ("honeymoon period").

Resulting in the clinical features below:

- **Classic triad 3P: Polyuria, Polydipsia & Polyphagia.**
- **Weight loss and weakness:** despite ↑ dietary intake, breakdown prevails over storage.
- **Severe insulin deficiency** may lead to diabetic **kectoacidosis lipolysis** → ↑ free fatty acids, which are oxidized to produce **ketone bodies** in the liver.
  - Rate of formation > rate of utilization of ketone bodies, resulting in **ketonuria & ketonemia.**
  - If there is **superimposed dehydration**, **metabolic ketoacidosis** results. The condition is life-threatening.
  - Infection, which ↑ insulin requirements, often precedes development of **diabetic ketoacidosis.**

Disturbance in insulin amount (ketoacidosis) → ↑ lipolysis → ↑ FFA in circulation which will be converted to keto acids → diabetic coma. (their **breath** will smell like ketones, sweet)

T2DM

The diagnosis is usually made after **routine serum or urine testing** in an asymptomatic but usually overweight patient.

- Manifests with polyuria and polydipsia, patients often are older than 40 years & obese.
- The metabolic derangements are much less severe. Patients in the decompensated state develop **hyperosmolar nonketotic coma**, which results from severe dehydration due to insufficient water intake in the face of polyuria (sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia).
  - Typically, the affected person is an elderly diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.
  - 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.

Any defect in the insulin pathway, sense secretion until the interaction of insulin with its receptors will lead to DM type 2

- **All other clinical features of both types are related to the complications of longstanding diabetes.**

Complications of Diabetes Mellitus:

The long term systemic complications are the same for the two major types of diabetes and are the major causes of morbidity and mortality in these patients.

Vascular system:

Diabetic Macrovascular Disease

Atherosclerosis

The hallmark of diabetic macrovascular disease is **severe accelerated atherosclerosis** in the aorta and large and medium-sized arteries. Myocardial infarction (caused by atherosclerosis of the coronary arteries), stroke, renal vascular insufficiency and gangrene of the lower limbs (as a result of advanced vascular disease) are responsible for ˜80% of deaths due to diabetes in adults.

Hyaline arteriosclerosis

Hyaline thickening of the wall of arterioles with narrowing of the lumen.

Remember: It's more prevalent and more severe in diabetics, but it is not specific for diabetes and may be seen in elderly persons who do not suffer from either diabetes or hypertension. Not surprisingly, in diabetic patients, its severity is related not only to the duration of the disease but also to the presence or absence of hypertension.

More common in the kidneys and eyes.

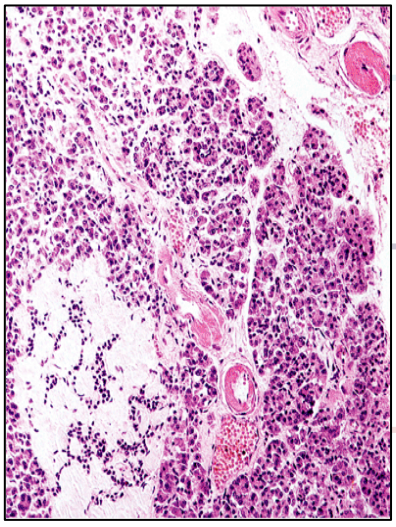
In the heart: The most commonly affected vessel by atherosclerosis is left anterior descending artery (coronary artery) → acute MI.
Ischemia in the leg → gangrene. (intermittent claudication: pain in the ischemic leg occurs when standing but is relieved by sitting)

Diabetic Microvascular Disease

- Responsible for many of the complications of diabetes, including renal failure (diabetic nephropathy), and Blindness (retinopathy), and some forms of neuropathy.
- The frequent occurrence of hypertension contributes to the development of the arteriolar lesions. In addition, deposition of basement membrane proteins, which may also become glycosylated, increases in diabetes.
- The effects of microvascular disease on tissue perfusion and wound healing are profound.
- ↓ blood flow to the heart, which is already compromised by coronary atherosclerosis.

Diabetic microangiopathy

Characterized by diffuse thickening of the capillary vascular basement membranes. Despite the increase in the thickness of basement membranes, affected vessels are more leaky to plasma proteins. The change is most evident in the capillaries of the skin, skeletal muscle, retina, kidney and may account for some of the changes seen in the peripheral nerves and placenta.



Arteriolosclerosis and capillary basement membrane thickening (by concentric layers of hyaline material composed of type IV collagen)

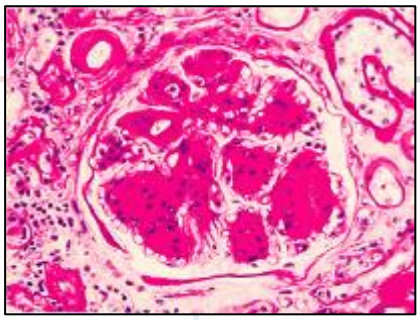
Healing of chronic ulcers that develop from trauma and infection of the feet in diabetic patients is commonly defective.

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

Diabetic nephropathy:

- 30- 40% of T1DM ultimately develop renal failure. A somewhat smaller proportion (up to 20%) of patients with T2DM are similarly affected.
- Diabetic nephropathy accounts for 1/3 of all new cases of renal failure.
- Prevalence ↑ with the severity and duration of the hyperglycemia.
- The earliest manifestation is the appearance of small amounts of albumin in the urine (greater than 30 but less than 300 mg/day—i.e., microalbuminuria).
- Kidney disease due to diabetes is the most common reason for renal transplantation in adults.
- The glomeruli in the diabetic kidney exhibit a unique lesion termed **Kimmelstiel-Wilson disease or nodular glomerulosclerosis.**

Vascular changes: renal atherosclerosis and hyaline arteriosclerosis (afferent & efferent arterioles)



Parenchymal changes: pyelonephritis[4] with ↑ propensity to develop necrotizing papillitis.

Glomerular changes: includes diffuse basement membrane thickening, nodular expansion of mesangial regions and exudative lesions.

Diffuse mesangial sclerosis	Nodular glomerulosclerosis
▪ A diffuse increase in mesangial matrix along with mesangial cell proliferation. ▪ Always associated with basement membrane thickening. ▪ Found in most individuals with disease of > 10 years' duration. ▪ When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome[5]. ▪ May be seen in association with old age and hypertension.	▪ A glomerular lesion made distinctive by ball-like deposits of a laminated matrix situated in the periphery of the glomerulus. ▪ These nodules are PAS-positive and usually contain trapped mesangial cells. ▪ Encountered in approximately 15% to 30% of persons with long-term diabetes and is a major contributor to morbidity and mortality. ▪ Essentially pathognomonic of diabetes, unless there is nephropathy.

Both forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular-appearing cortical surface.

[4] An acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to involve the tubules. One special pattern is necrotizing papillitis.

[5] Characterized by proteinuria, hypoalbuminemia, and edema.

Diabetic retinopathy:

- The most devastating ophthalmic complication of diabetes.
- The most important cause of blindness in the Unites States in persons under the age of 60 years. The risk is higher in T1DM than in T2DM.
- 10% of patients with T1DM of 30 years' duration become legally blind. There are many more patients with T2DM, so these are the most numerous patients with diabetic retinopathy.
- Diabetics also have ↑ propensity for glaucoma and cataract formation, both of which contribute to visual impairment.
- **Can be non-proliferative (background) or proliferative.**

Non-proliferative changes	Proliferative changes
▪ **Microangiopathy**[6] in the retinal blood vessels (leads to loss of capillary pericytes) with development of **micro aneurysms**[7] ▪ **Retinal hemorrhages (blots).** ▪ **Retinal edema**: from excessive capillary permeability. ▪ **Exudates (cotton wool spots)**: Can be either "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids in retina) ▪ **Venous dilatation:** Tend to occur at focal points of weakening, resulting from loss of pericytes.	**Neovascularization and fibrosis,** which may lead to **retinal detachment** (Vitreous hemorrhages can result from rupture of newly formed capillaries; the subsequent organization of the hemorrhage can pull the retina off its substratum) and **blindness** (especially if it involves the macula).

- Proliferative: neoangiogenesis + exudate → fibrosis → retinal detachment → sudden blindness.
  Proliferative: Newly formed blood vessels
- Nonproliferative: exudate due to vasculopathy (cotton wool spots/appearance by fundoscopy)

Diabetic neuropathy:

The most common and distressing complications of diabetes.

- Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.
- Affects Sensory and Autonomic Innervations, peripheral sensory impairment, and autonomic nerve dysfunction.
- Changes in the nerves are complex, and abnormalities in axons, the myelin sheath, and Schwann cells have all been found.
- Plays a role in the painless destructive joint disease that occasionally occur.

[6] Thickening of the capillary basement membrane
[7] Discrete saccular dilations of retinal choroidal capillaries that appear through the ophthalmoscope as small red dots).

Polyneuropathy

- Symmetric peripheral neuropathy (most frequent), affecting both motor and sensory nerves (begins with the lower extremities then over time extending to the upper extremities "glove & stocking" pattern)
- Characterized by pain and abnormal sensations in the extremities.
- Can lead to **foot ulcers**.

Autonomic neuropathy

- May cause impotence with bladder and bowel dysfunction.
- Diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop or isolated cranial nerve palsies.

- Stroke (most commonly in middle cerebral a.)
-Hypertension leading to intra cerebral haemorrhage which causes death.
Neuropathy:
Can be sensory, motor or both.
Characterized by parasthesia (loss of sensation), pain in their legs (either due to intermittent claudication العرج المتقطع or continuous)
Minor trauma can lead to ulcers (patient doesn't feel the minor trauma)

Infections:

People with diabetes have an ↑ tendency to develop infections.

- Bacterial & Fungal Infections occur in poorly controlled diabetic hyperglycemia.
- Renal papillary necrosis may be a devastating complication of bladder infection.
- Enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis.
- 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)
- **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.

They get infections because of weak phagocytosis & weakness of immunity
Gangrene of the lower limb happens due to vasculopathy (eg. severe atherosclerosis and obliteration); most patients that present with gangrene have neuropathy as well (they don't feel pain) (mostly in lower limbs)

Skin complications:

E.g. necrobiosis lipoidica diabeticorum and granuloma annulare.

Pregnancy:

Pregnant women with diabetes are at a higher risk of developing pre-eclampsia and tend to have large babies.

Further Reading: **(Read it just in case)**

DM other forms:

- **Gestational diabetes:** Develops in a few percent of pregnant women, owing to the insulin resistance of pregnancy combined with a B-cell defect, but almost always abates following parturition.
  - May put both mother and fetus at risk.
  - It may continue after parturition in a small proportion of these patients.
  - These women highly susceptible to overt T2DM later in life.
- Can also occur **secondary to other endocrine conditions** or drug therapy, especially in patients with Cushing's syndrome or during treatment with glucocorticoids.

Figure 19–31 Nephrosclerosis in a patient with long-standing diabetes. The kidney has been bisected to demonstrate both diffuse granular transformation of the surface (*left*) and marked thinning of the cortical tissue (*right*). Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst (*far right*).

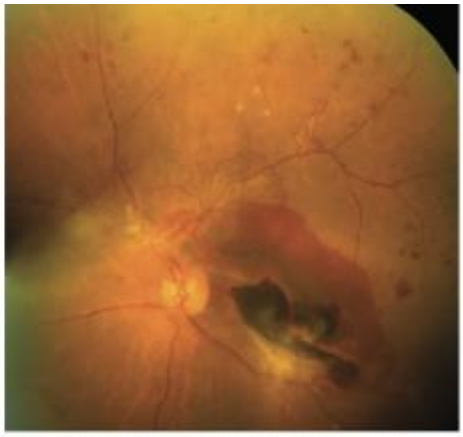


Figure 19–32 Characteristic morphologic changes of diabetic retinopathy. Features include advanced proliferative retinopathy with retinal hemorrhages, exudates, neovascularization, and tractional retinal detachment (*lower right corner*).
(Courtesy of Dr Rajendra Apte, Washington University School of Medicine, St. Louis, Missouri.)

What are the main signs and symptoms of DM?
Polyuria, polyphagia and polydipsia, these symptoms are more with DM type 1 in addition to weight loss, dehydration and ketoacidosis.
While DM type 2 mainly the patients have obesity.

DM T2 Pathogenesis:

Two metabolic mechanisms have been postulated:

1. **Obesity and Insulin resistance:**

   Insulin resistance is present even with **simple obesity unaccompanied by hyperglycemia**, indicating a fundamental abnormality of insulin signaling in states of **fatty excess**.

   Some of the leading causes of insulin resistance has increased substantially:

   ***Role of excess free fatty acids* (FFAs):**

   Intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state

   Role of inflammation:

   It is now known that a permissive inflammatory milieu (mediated *not* by an autoimmune process as in type 1 diabetes but rather by pro- **inflammatory cytokines** that are secreted in response to excess nutrients such as FFAs) results in both peripheral insulin resistance and **beta cell dysfunction. (**cytokine interleukin IL-1β)

   Role of adipokines*[8]*:

   Adipocytes also release IL-1β and other pro- inflammatory cytokines into the circulation in response to excess FFAs which promote peripheral insulin resistance

   Peroxisome proliferator-activated receptor-γ (PPARγ):

   It's nuclear receptor and transcription factor expressed in adipose tissue and plays a seminal role in adipocyte differentiation.

   Activation of PPARγ promotes secretion of **antihyperglycemic adipokines** such as adiponectin.

   A class of antidiabetic medications known as **thiazolidinediones** acts as **agonist ligands** for PPARγ and improves insulin sensitivity.

[8] Adipose tissue is not merely a passive storage depot for fat; it can operate as a functional endocrine organ, releasing so-called adipokines in response to extracellular stimuli or changes in metabolic status.

2. **Beta cell dysfunction** (inadequate insulin secretion in the face of insulin resistance and hyperglycemia).

   As we mentioned in the causes of Peripheral insulin resistance; excess nutrients such as FFAs and glucose can → the secretion of pro-inflammatory cytokines from beta cells → recruitment of macrophages and T cells into the islets → more local cytokine production.

   Amyloid replacement of islets is a characteristic finding in persons with *long-standing* type 2 diabetes and is present in more than 90% of diabetic islets examined.

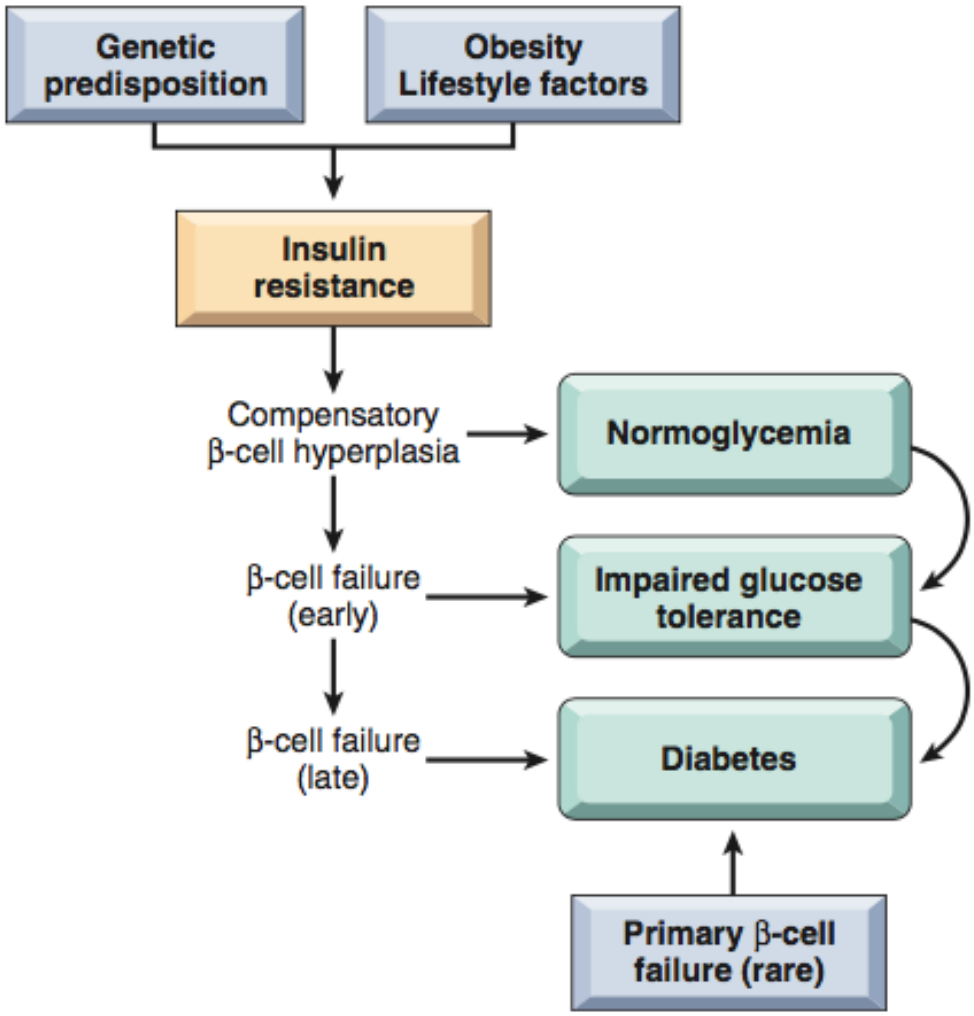


Figure 19–23 Pathogenesis of type 2 diabetes mellitus. Genetic predisposition and environmental influences converge to cause insulin resistance. Compensatory beta cell hyperplasia can maintain normoglycemia, but eventually beta cell secretory dysfunction sets in, leading to impaired glucose tolerance and, ultimately, frank diabetes. Rare instances of primary beta cell failure can lead directly to type 2 diabetes without an intervening state of insulin resistance.

T1DM:

Exogenous insulin requirements may be minimal to none, why? Because of residual ongoing endogenous insulin secretion, but thereafter the beta cell reserve is exhausted and insulin requirements increase dramatically.

How do the clinical features of T1DM take place?

Polyuria:

Hyperglycemia exceeds the renal threshold for reabsorption → glycosuria → osmotic diuresis → *polyuria* → loss of water and electrolytes.

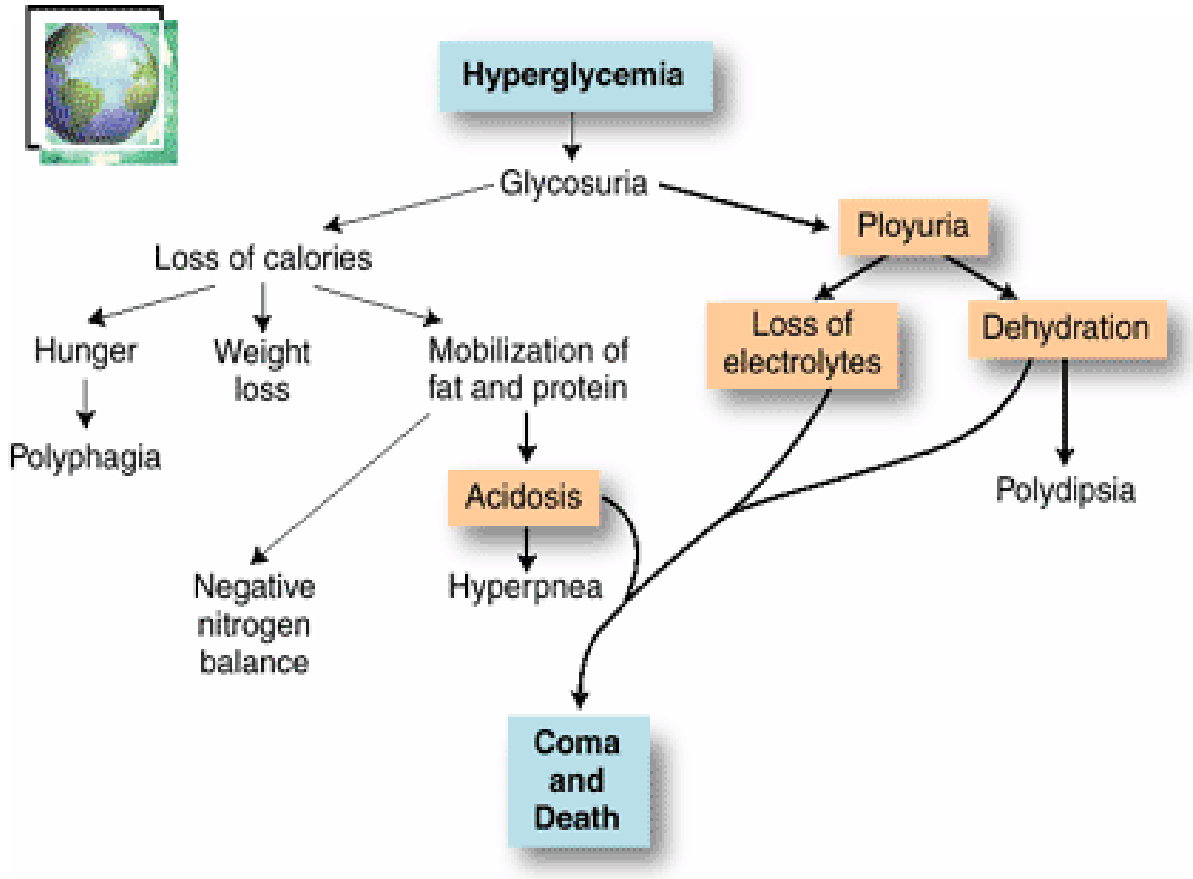
Polydipsia:

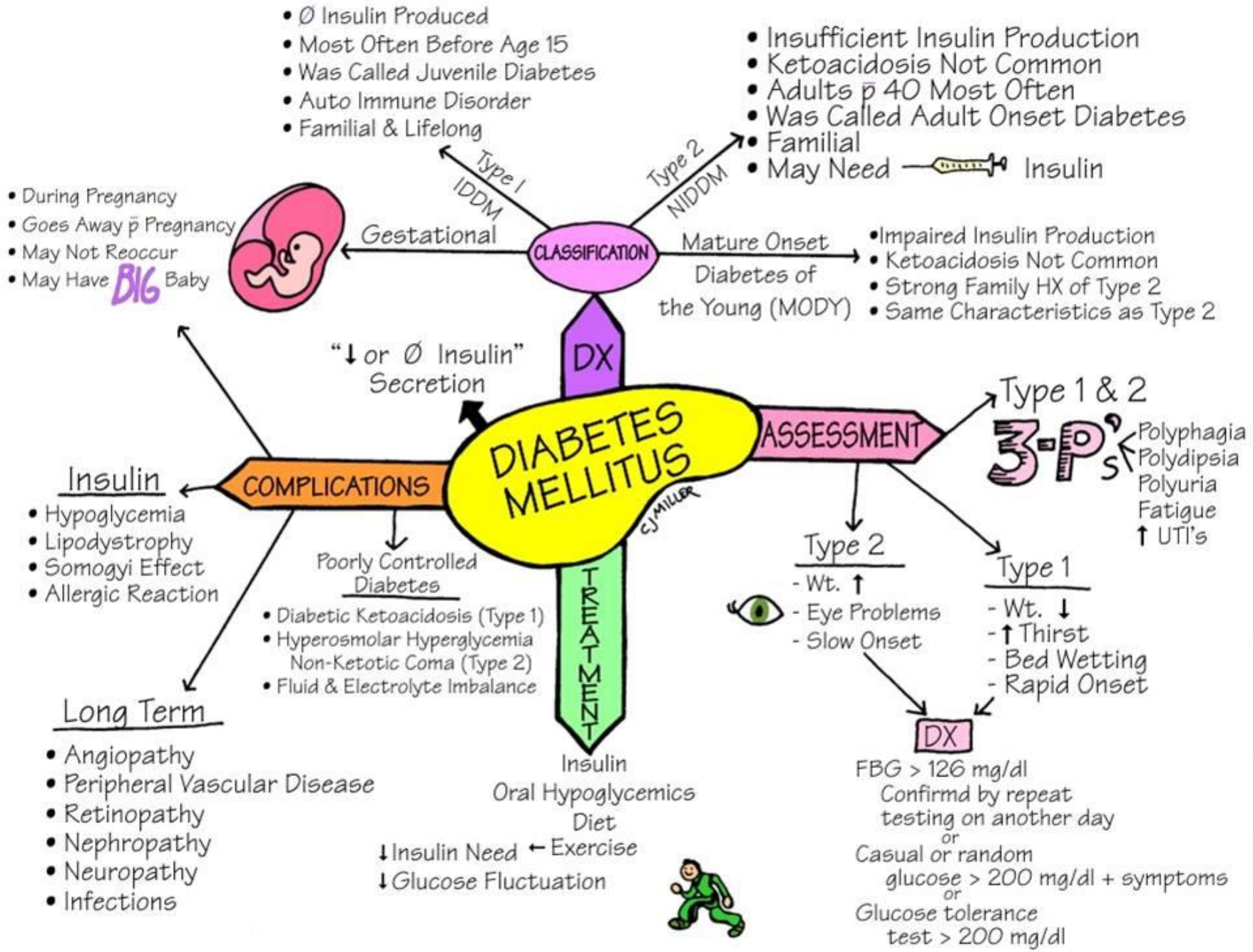
The obligatory renal water loss + the extracellular hyperosmolarity resulting from the ↑ levels of glucose in the blood → osmotic depletion of intracellular water → triggering osmoreceptors of the thirst centers of the brain → intense thirst (*polydipsia*).

Polyphagia:

Breakdown of proteins & fats for gluconeogenesis ↑ appetite. How?

Deficiency of insulin → catabolism of proteins & fats (negative energy balance) →Proteolysis → gluconeogenic amino acids are removed by the liver & used as building blocks for glucose.





Comparison between pathology of T1DM & T2DM:

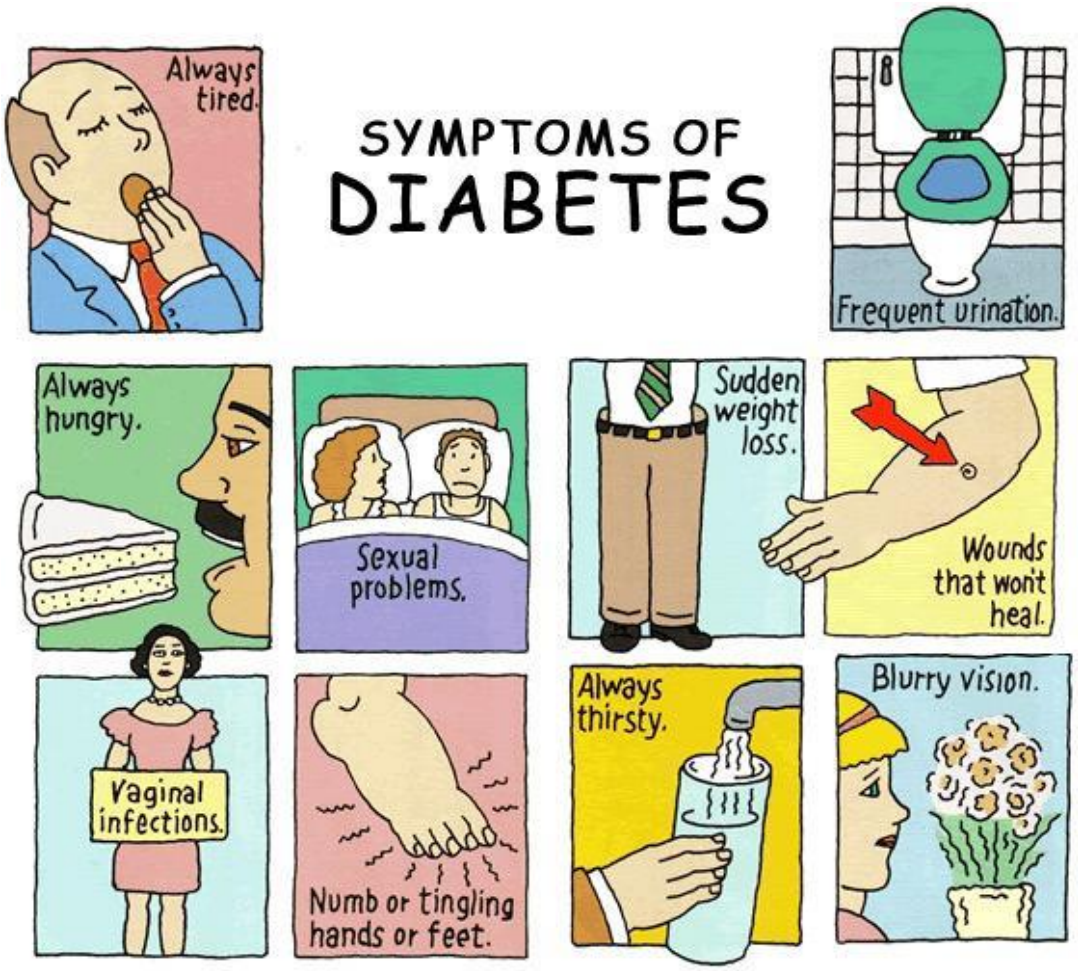
Type 1	Type 2
Usually before 30	After 30
Abrupt; symptomatic (polyuria, polydipsia, dehydration); often severe with ketoacidosis	Gradual; usually subtle
Normal weight; recent weight loss is common	Overweight
Genetics <20%	>60%
Monozygotic Twins 50% concordant	90% concordant
HLA Association, ABS to islet cell AG +	No
Histopathology: Early—inflammation | Late—atrophy and fibrosis	Histopathology: Late- Fibrosis, amyloid
B-cell mass: Markedly reduced	Normal or slightly reduced
Insulin levels: Markedly reduced	Elevated or normal

	T1DM	**T2DM**
Leukocytic infiltration of the islets,	Early in the disease More severe	Early in the disease
reduction in the number of B- cells.	Seen	Not seen
Amyloid replacement of islets	Not seen	in long-standing cases
<u>Fibrosis</u>	Uncommon	fibrous tissue accumulates, sometimes to such a degree that they are obliterated.

Table 19–6 Type I Versus Type 2 Diabetes Mellitus

Type I 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	
Dysfunction in regulatory T cells (Tregs) leading to 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"	*Early*: inflammation; *late*: amyloid deposition in islets
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, human leukocyte antigen; MHC, major histocompatibility complex.



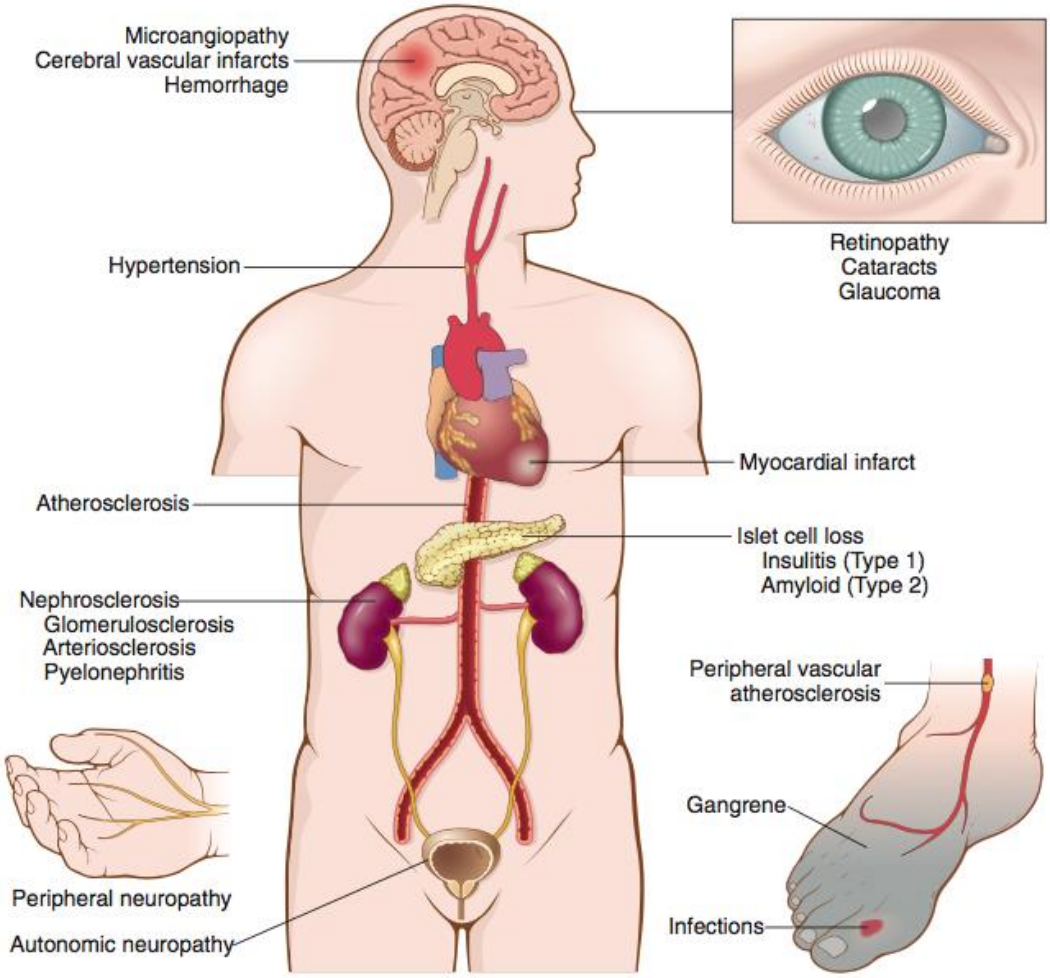


Figure 19–25 Long-term complications of diabetes.

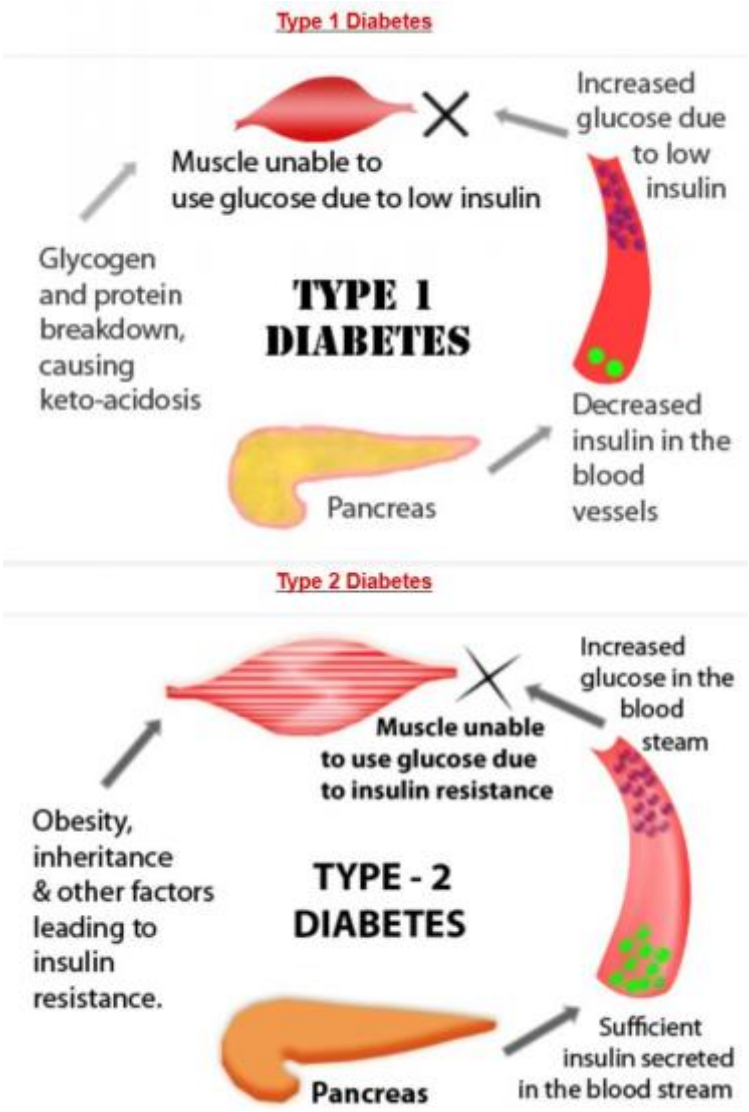


Table 19–5 Classification of Diabetes Mellitus

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

Modified from the American Diabetes Association: Position statement from the American Diabetes Association on the diagnosis and classification of diabetes mellitus. Diabetes Care 31(Suppl 1):S55–S60, 2008.

Check Your Understanding

MCQs:

1. **A 15 years old male is brought by his mother to the family doctor. The mother noticed that her son drinks a lot of water and goes to the bathroom more frequently. Which of the following changes would most likely be seen in microscopy of the pancreas?**
   A. Leukocytic infiltration of the islets
   B. Reduction in the number of B- cells.
   C. Amyloid replacement of islets
   D. Fibrosis
   E. Both a & b are correct

2. **Myocardial infarction in diabetes is a complication of:**
   A. Diabetic macrovascular disease
   B. Diabetic microvascular disease
   C. Diabetic nephropathy
   D. Diabetic retinopathy
   E. Diabetic neuropathy

3. **Blindness is a result of:**
   A. Diabetic macrovascular disease
   B. Diabetic microvascular disease
   C. Diabetic nephropathy
   D. Diabetic retinopathy
   E. Diabetic neuropathy

4. **Glomerular changes in diabetic nephropathy include:**
   A. Diffuse basement membrane thickening
   B. Nodular expansion of mesangial regions
   C. Exudative lesions
   D. necrotizing papillitis.
   E. A, B, and C are correct

5. **What is a primary cause of diabetic complication including; retinopathy, nephropathy and peripheral neuropathy:**
   A. Low immunity
   B. Microangiopathy
   C. Atheroma
   D. Systemic disturbances

1.E 2.A 3.B 4.E 5.B

6. **Long-term complications of diabetes include _____.**
   A. Increased risk for kidney failure
   B. Impaired sensation in the hands and feet
   C. Increased risk for high blood pressure and atherosclerosis
   D. All the complications listed are correct.

7. **Type 2 diabetes can be prevented or delayed through _____.**
   A. Lifestyle interventions
   B. Weight loss
   C. Exercise
   D. All of the options listed are correct

8. **The MOST common cause of death is _____**
   A. Renal diseases
   B. Retinopathy
   C. Myocardial Infraction
   D. Skin infection

9. **What are the most affected organs by diabetes?**
   A. Eyes, kidneys and nerves
   B. Stomach and kidneys
   C. Skeletal muscles and eyes
   D. Eyes and small intestines

10. **Diabetes is the leading cause of:**
   A. Cardiovascular diseases
   B. Lung diseases
   C. Stomach cancer
   D. End stage renal disease

6.D 7.D 8.C 9.A 10. D

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
