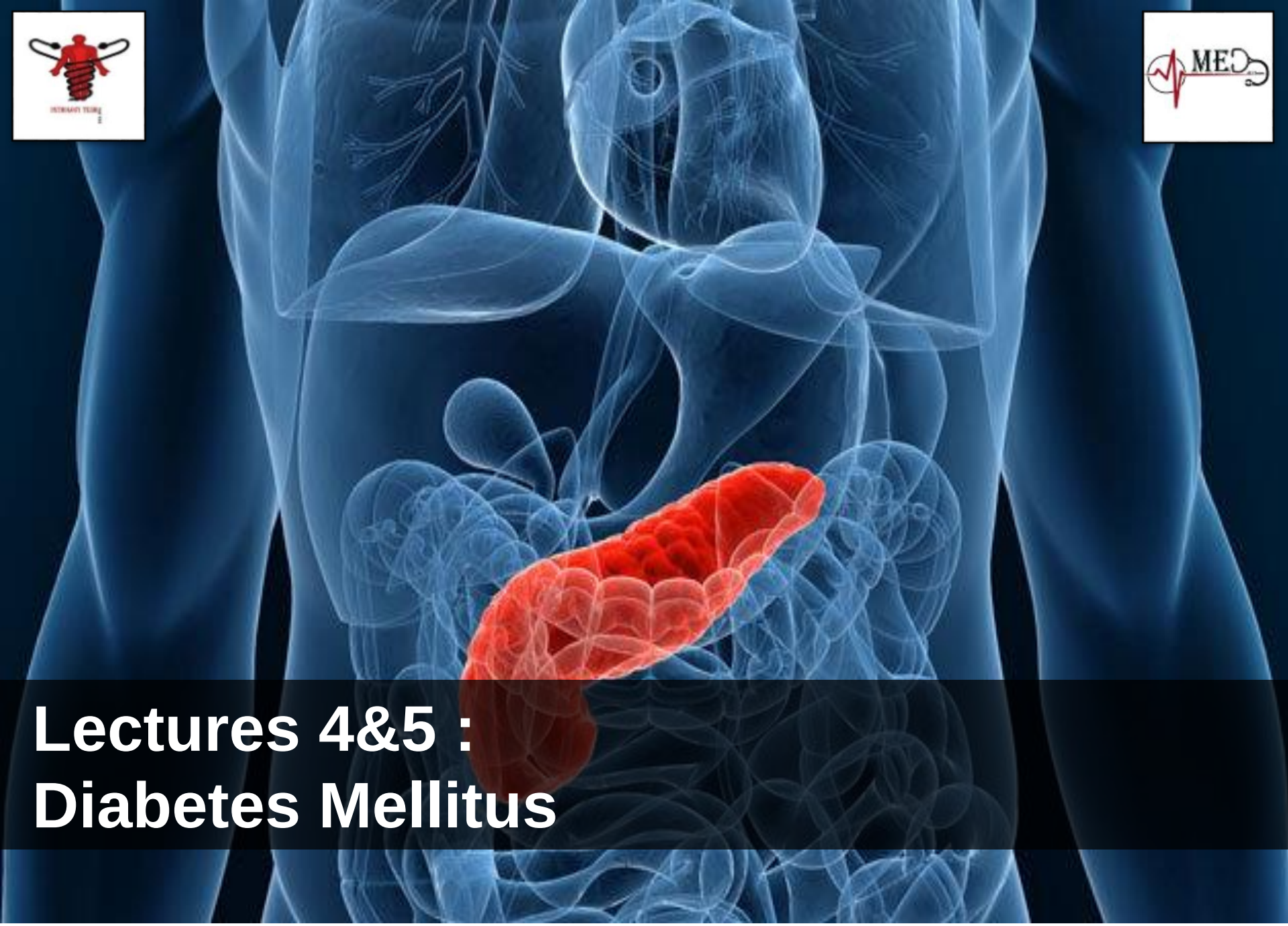
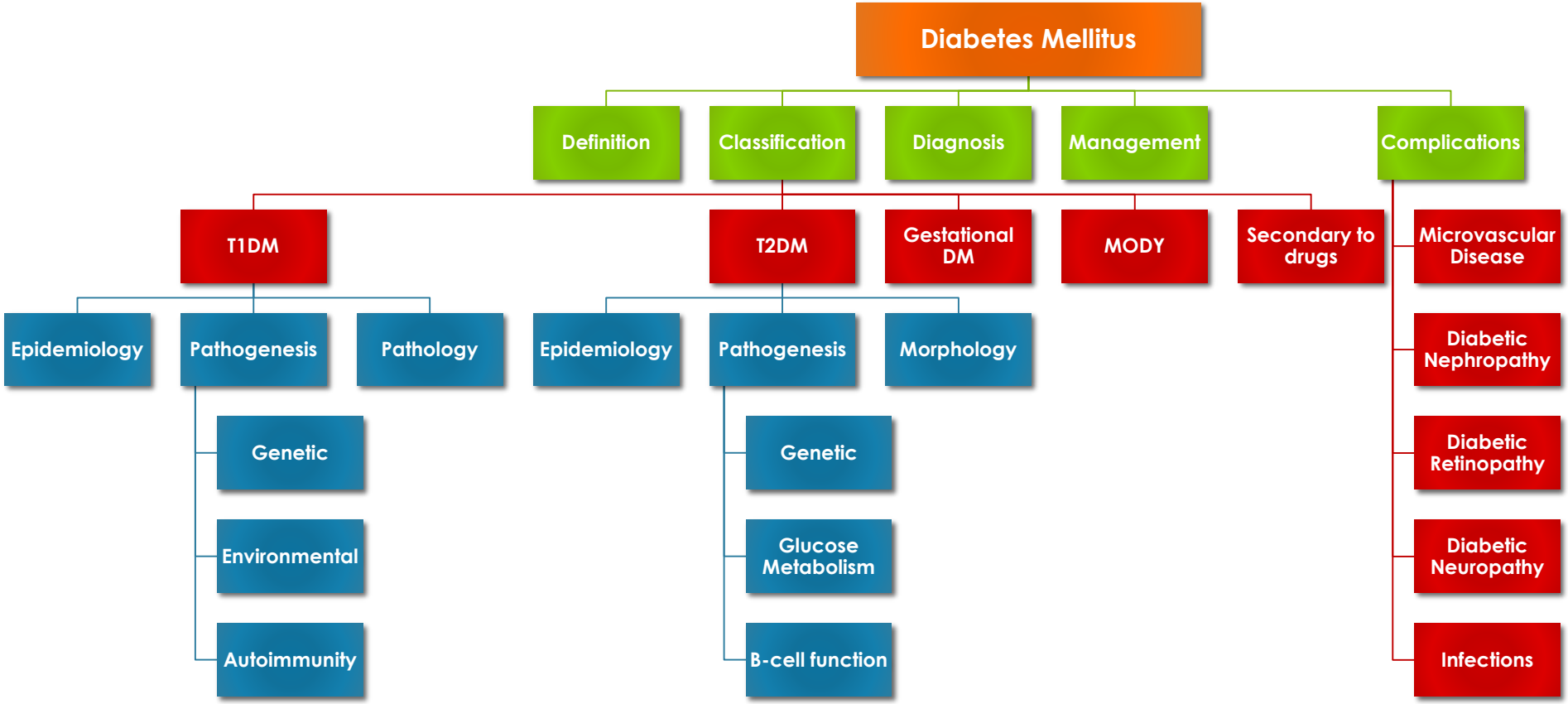


Lectures 4&5 : Diabetes Mellitus

▫ Important ▫ Notes ▫ Explanation

Objectives

- ✓ Understand the pathogenesis and major histopathological changes seen in diabetes mellitus type 1 and type 2.
- ✓ Recognize the major complications of diabetes mellitus.


Diabetes Mellitus
Definition
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Epidemiology
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Genetic
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Diabetic Retinopathy
Diabetic Neuropathy
Infections

Overview

Sir William Osler defined diabetes mellitus as

"a syndrome due to a disturbance in carbohydrate metabolism from various causes, in which sugar appears in the urine, associated with thirst, polyuria, wasting and imperfect oxidation of fats."

- Group of metabolic disorders sharing the common underlying feature of hyperglycemia.
- Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and non-traumatic lower extremity amputations.
- Two major forms of diabetes mellitus are recognized, distinguished by their underlying pathophysiology.

Classification of DM

1. Type 1 diabetes :

β-cell destruction, usually leading to absolute insulin deficiency.

2. Type 2 diabetes :

combination of insulin resistance and β-cell dysfunction.

3. Genetic defects of β-cell function : (more of a type 2 in the young)

-Maturity-onset diabetes of the young (MODY), caused by mutations in:

- **MODY1:** Hepatocyte nuclear factor 4a (HNF4A).
- **MODY2:** Glucokinase (GCK).
- **MODY3:** Hepatocyte nuclear factor 1a (HNF1A).
- **MODY4:** Pancreatic and duodenal homeobox 1 (PDX1).
- **MODY5:** Hepatocyte nuclear factor 1β (HNF1B) ,also known as, (transcription factor 2 (TCF2)).
- **MODY6:** Neurogenic differentiation factor 1 (NEUROD1).

4. Genetic defects in insulin action :

Type A insulin resistance, Lipoatrophic diabetes, including mutations in PPARG.

5. Exocrine pancreatic defects :

Chronic pancreatitis, Neoplasia, Cystic fibrosis …

7. Infections :

CMV, Coxsackie B virus, Congenital rubella.

8. Drugs :

Glucocorticoids, Thyroid hormone, Interferon-a, β-adrenergic agonists…

9. Genetic syndromes associated with diabetes :

Down's, Kleinfelter syndrome, Turner syndrome, Prader-Willi syndrome.

10. Gestational diabetes mellitus.

Forms of DM

1) Type 1 diabetes mellitus (T1DM) :

- Formerly known as insulin-dependent (IDDM) or juvenile-onset diabetes.

- Caused by autoimmune destruction of the insulin-producing B-cells in the pancreatic islets of Langerhans.

- Affects less than 10% of all patients with diabetes.

2) Type 2 diabetes mellitus (T2DM) :

- Formerly known as non–insulin-dependent (NIDDM) or maturity-onset diabetes.

- Typically associated with obesity and results from a complex interrelationship between resistance to the metabolic action of insulin in its target tissues and inadequate secretion of insulin from the pancreas.
- Affects approximately 90% of all patients with DM.

3) 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.

4) Maturity-onset diabetes of the young (MODY) :

- Rare autosomal dominant form of inherited diabetes.

Associated with a variety of gene defects that affect B-cell function, including glucokinase, an important sensor for glucose metabolism within the B-cell, and several mutations in genes that control the development and function of the B-cells.
Manifestation is similar to T2DM but at earlier age (onset similar to T1DM).
- It is more common than before due to contribution of environmental factors and lifestyle.
- Mutations in these genes, however, do not account for the typical prevalent forms of T2DM.

5) Diabetes can also occur secondary to other endocrine conditions or drug therapy, especially in patients with Cushing's syndrome or during treatment with glucocorticoids.

Type 1&2 DM

	Type 1 DM	Type 2 DM
- Age **- Onset of DM**	- Usually before 20. -Abrupt; symptomatic (polyuria, polydipsia, dehydration); often sever with ketoacidosis.	- Usually after 30 - Gradual; usually subtle.
weight	Normal weight ; recent weight loss is common.	Overweight
Genetics	- <20% - Monozygotic Twins 50% concordant.	- > 60%. - > 90% concordant.
HLA association	**HLA association**, autoantibodies to beta cell antigens.	No
Histopathology	- Early → inflammation. - Late → atrophy and fibrosis.	- Early → NO changes. - Late → Fibrosis, amyloid.
B- cell mass	Markedly reduced	Normal or slightly reduced
Insulin levels	Markedly reduced.	*Elevated or normal.

*Early, It will be elevated as a compensation for resistance then it will be decreased .

Type 1 Diabetes Mellitus

Autoimmune destruction of the B cells in the islets of Langerhans. And characterized by :

1. Few if any functional B cells in the islets of Langerhans.
2. 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 and leads to glucosuria and dehydration from loss of body water into the urine.
- Always glucose urea induces polydipsia, dehydration, loss of calories, polyphagia, negative nitrogen balance and polyuria.
- If uncorrected, the progressive acidosis and dehydration ultimately lead to coma and death.

Epidemiology :

- T1DM is 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.
- Some older patients may present with autoimmune B-cell destruction that has developed slowly over many years.
- An increased incidence in late fall and early winter has been documented in many geographical areas.

Pathogenesis :

Represents interplay of genetic susceptibility, autoimmunity and environmental factors.

1- Genetic Factors :

- genome-wide association studies have identified multiple genetic susceptibility loci for type 1 diabetes, as well as for type 2 diabetes.
- For type 1 diabetes the most important is the HLA locus on chromosome 6p21.
- 90 - 95% of Caucasians with this disease have either a HLA-DR3 or HLA-DR4 haplotype (N: 30-40%).
- 40 - 50% of type 1 diabetics are combined DR3/DR4 heterozygotes (Normal 5%)
- Several non-HLA genes also confer susceptibility to type 1 diabetes.
- Fewer than 20% of those with T1DM have a parent or sibling with the disease.
- Monozygotic twins : 50% concordant
- The children of diabetic fathers with T1DM are three times more likely to develop the disease than are children of diabetic mothers.

2- Environmental Factors :

- Viruses and chemicals, CMV, Mumps and group B Coxsackie, Rubella viruses.
- Geographical and seasonal differences in the incidence of T1DM further suggest that environmental factors are important in its pathogenesis.

3- Autoimmunity :

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 (Inflammation of the pancreas in the early stage of diabetes).

- Cell-mediated immune mechanisms are fundamental to the pathogenesis of T1DM ,CD8+T lymphocytes pre-dominate, although 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.
- An autoimmune origin for T1DM was initially suggested by the demonstration of circulating antibodies against components of the B cells (including insulin itself) in most newly diagnosed children with diabetes.
- The autoimmunity in some T1DM can be predictable by measuring these antibodies in the peripheral blood.
- Many patients develop islet cell antibodies months or years before insulin production decreases and clinical symptoms appear.
- Detection of serum antibodies to islet cells and certain islet antigens remains a useful clinical tool for differentiating between type 1 and type 2 diabetes
- The destruction of B-cells in T1DM generally develops slowly over years.

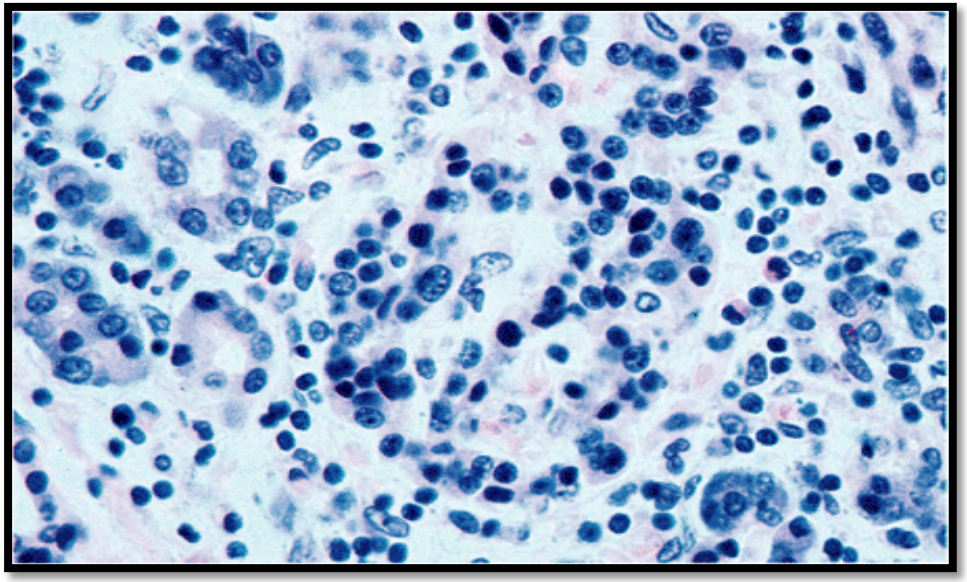
REMEMBER :

- CD4 are the T-cell helper.
- CD8 are the T-cell suppressor or CYTOTOXIC
- CD4 : CD8 = 2 : 1 (Normally) | 1 : 2 in T1DM.

- **T cell attack immediately, interleukin secretion, lymphocyte B also attack. So, the mechanism is both *humoral* and *T cell*.**

Pathology of Type 1 DM :

- Lymphocytic infiltrate in the islets (insulitis), sometimes accompanied by a few macrophages and neutrophils. The major inflammatory cells infiltrate are lymphoplasma cells.
- As the disease becomes chronic, the B cells of the islets are progressively depleted of Beta cells.
- Fibrosis of the islets is uncommon.
- In contrast to T2DM, deposition of amyloid in the islets of Langerhans is absent in T1DM.
- The exocrine pancreas in chronic T1DM often exhibits diffuse interlobular and interacinar fibrosis, accompanied by atrophy of the acinar cells.



Insulitis

Type 2 Diabetes Mellitus

Epidemiology :

- Almost 10% of persons older than 65 years of age are affected.
- The disease usually develops in adults, with an increased prevalence in obese people (80% of patients with T2DM are overweight).
- Recently, T2DM has been appearing in increasing numbers in younger adults and adolescents, because of worsening obesity and lack of exercise.

Pathogenesis :

- Complex interplay between underlying **resistance to the action of insulin** in its metabolic target tissues and reduction in glucose-stimulated insulin secretion.
- Progression to overt diabetes in susceptible populations occurs most commonly in patients exhibiting both of these defects.

1- Genetic Factors :

- Multi-factorial, and the inheritance pattern is complex and thought to be due to multiple susceptible genes.
- No association with genes of the major histocompatibility complex (MHC), as seen in T1DM.
- 60% of patients have either a parent or a sibling with the disease (runs in families).
- Among monozygotic twins, both are almost always affected.
- Constitutional factors such as obesity (which itself has strong genetic determinants), **hypertension**, and the amount of exercise influence the phenotypic expression of the disorder.

2- Glucose metabolism :

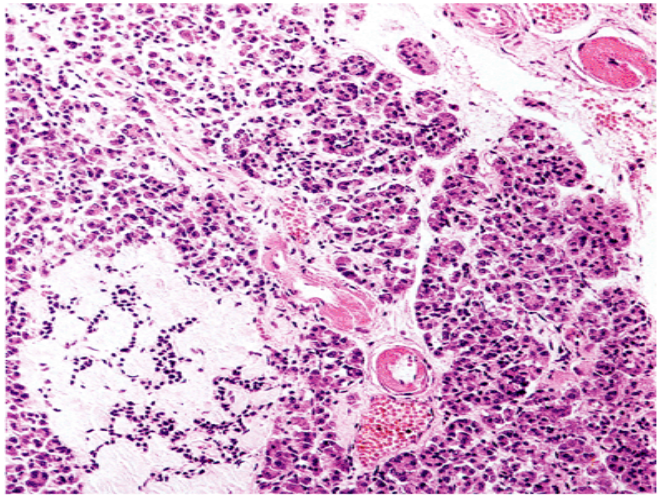
- In a normal person, the extracellular concentration of glucose in fed and fasting states is maintained in a tightly limited range mediated by the opposing actions of insulin and glucagon.
- Following a carbohydrate-rich meal, absorption of glucose from the gut leads to an increase in blood glucose, which stimulates insulin secretion by the pancreatic **β**-cells and the consequent insulin-mediated increase in glucose uptake by skeletal muscle and adipose tissue.
- At the same time, insulin suppresses hepatic glucose production.
- In diabetic patient, the equalizer between glucagon & insulin is lost. Insulin can't suppress glucose production from the liver, leading to hyperglycemia..

3- β-Cells function :

- Persons with T2DM exhibit impaired **β**-cell insulin release in response to glucose stimulation
- This functional abnormality is specific for glucose, since the **β**-cells retain the ability to respond to other stimulants, such as amino acids.
- **β**-cell function may also be affected by the chronically elevated plasma levels of free fatty acids that occur in obese persons.
  (Fatty acids accumulate in cells disturbing insulin cell signaling causing insulin resistant)

Morphology :

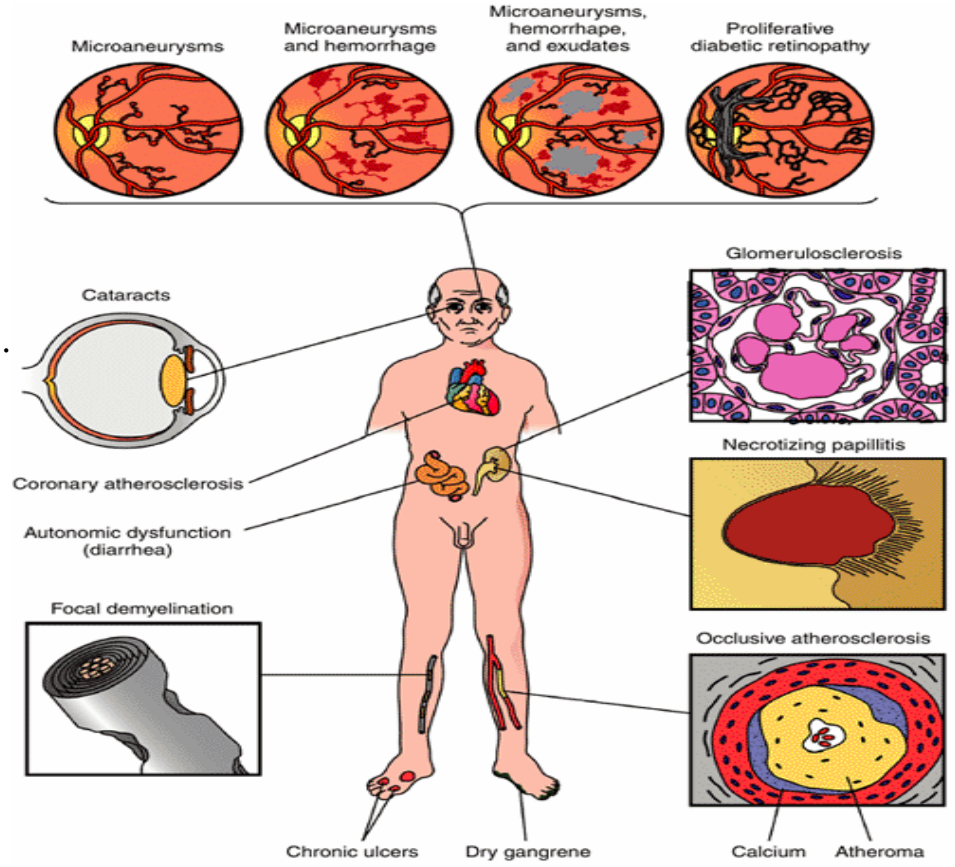
- No consistent reduction in the number of **β**-cells
- No morphologic lesions of B- cells
- In some islets, **fibrous** tissue accumulates, sometimes to such a degree that they are obliterated.
- Islet **amyloid** is often present particularly in patients over 60 years of age. (so can be detected by Congo Red stain)



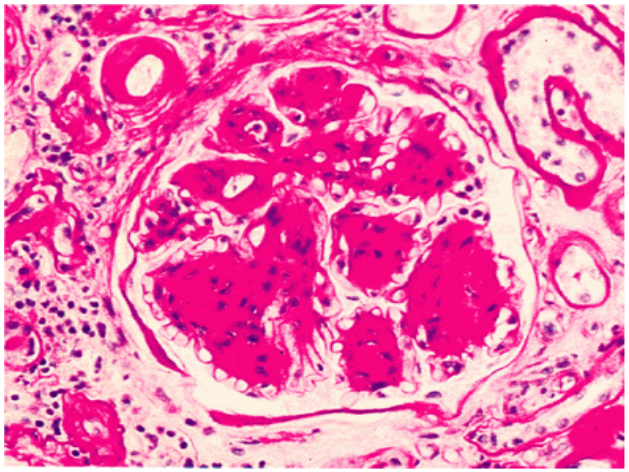
Complications of Diabetes :

1- Diabetic Microvascular Diseases :

- Responsible for Many of the Complications of Diabetes, Including Renal Failure and Blindness
- Arteriolosclerosis and capillary basement membrane **thickening** are characteristic vascular changes in diabetes. (**sclerosis** in large blood vessels, **hyalinosis** in small ones)
- 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.
- (AGEs binds to plasma proteins and accumulate in basement membrane of blood vessels and glomeruli causing their thickness)
- Aggregation of platelets (thrombi formation) in smaller blood vessels and impaired fibrinolytic mechanisms have also been suggested as playing a role in the pathogenesis.
- The effects of microvascular disease on tissue perfusion and wound healing are profound.
- Reduce blood flow to the heart, which is already compromised by coronary atherosclerosis.
- **Defective healing** of chronic ulcers that develop from trauma and infection of the feet in diabetic patients due to hypoperfusion.



2- Diabetic Nephropathy :



- 30% to 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 one third of all new cases of renal failure.
- The prevalence of diabetic nephropathy increases with severity and duration of the hyperglycemia.
- 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.
- 2 important pathological features: thickening of the basement membrane of the glomeruli & **nodular glomerulosclerosis.**

3- 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
- Diabetic nephropathy and retinopathy could be caused by microvascular diseases, AGEs and sorbitol pathway is related.
- At the beginning, you'll see microaneurysm (small dilatations in the wall) > hemorrhage > exudate > diabetic retinopathy.

4- Diabetic Neuropthy : (The most common & distressing complications of diabetes)

- Changes in the nerves are complex, and abnormalities in axons, the myelin sheath, and Schwann cells have all been found.
- Characterized by pain & abnormal sensations in the extremities or no pain at all.
- Plays a role in the painless destructive joint disease that occasionally occur.
- Microvasculopathy in the vessels of nerves contributes to the disorder
- Affects Sensory and Autonomic Innervations, causing peripheral sensory impairment and autonomic nerve dysfunction
- Peripheral neuropathy can leads to foot ulcers.

5- Infections :

- Bacterial and Fungal Infections Occur in Diabetic hyperglycemia if poorly controlled. (Some microorganisms feed in glucose, so hyperglycemia is good envirnoment for them + in addition to the low inmmunity in the diabetics)
- Renal papillary necrosis may be a devastating complication of bladder infection.
- Mucormycosis: A dangerous infection complication of poorly controlled diabetes is often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.

Gestational Diabetes :

- Diabetes Occurring During Pregnancy
- May Put both Mother and Fetus at risk
- Develops in only a few percent of seemingly healthy women during pregnancy.
- It may continue after parturition (As T2DM) in a small proportion of these patients.
- These women highly susceptible to overt T2DM later in life.
- Pregnancy is a state of insulin resistance. (Could be due to hormones secreted from placenta that block the action of insulin)

Diagnosis of DM

Any one of three criteria :

1- A random glucose concentration greater than **200 mg/dL**, with classical signs and symptoms .

2- A fasting glucose concentration greater than **126 mg/dL** on more than one occasion.

(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.". Pre-diabetic individuals have a significant risk of progressing to overt diabetes over time and cardiovascular disease.)

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.

Management

Type 1 :

- Insulin absolutely required.

Type 2 :

- Lifestyle modification; diet, exercise, oral hypoglycemic, often insulin supplement needed later.

Summary
(from Robbin's basic pathology)

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), probably mediated by cytokines released from adipose tissues (adipocytokines). Other players in the *adipo-insulin axis* include FFAs (which may cause *lipotoxicity*) and the PPARγ receptor, which modulates adipocytokine levels.
- Monogenic forms of diabetes are uncommon and are caused by single-gene defects that result in primary beta cell dysfunction (e.g., *glucokinase* mutation) or lead to abnormalities of insulin–insulin receptor signaling (e.g., insulin receptor gene mutations).
- The long-term complications of diabetes are similar in both 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.

Thank You!

We hope you found this helpful and informative.

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