429 pathology team represents:

Diabetes Mellitus 1& 2

((extra notes are in Gray))

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Diabetes Mellitus:

Sir William Osler – most influential physician of history - defined diabetes mellitus as
"a syndrome due to a disturbance in carbohydrate metabolism from various causes, in which sugar appears in the uri
associated with thirst, polyuria, wasting and imperfect oxidation of fats."
→ *rise in glucose level in plasma*

Major Forms:

DM Type I	DM Type II
Formerly known as insulin-dependent (IDDM) or juvenile-onset diabetes. Caused by autoimmune destruction of the insulin-producing Beta-cells in the pancreatic islets of Langerhans. Affects less than 10% of all patients with diabetes	Formerly known as : non–insulin-dependent(NIDDM)or maturity-onset diabetes. Typically associated with obesity. Results from a complex interrelationship between: 1- *Resistance* to the metabolic action of insulin in its targe tissues. 2- *Inadequate secretion* of insulin from the pancreas.
In Childhood (before 20)	**In** Adolescence (after 30)
SUDDEN **ONSET** (abrupt) Symptomatic: Poly triad (polyuria, polydipsia, polyphagia) Severe with *Ketoacidosis*	GRADUAL **ONSET** (subtle)
Genetically more than 20% 50% predisposition in *Monozygotic twins* - less genetic -	**Genetically** less than 60% 90% predisposition in *Monozygotic twins* - more genetic -
Mutation in HLA → Antibodies to *islet cells* (an autoimmune reaction toward endocrine pancreas)	Usually no **mutations** (no HLA)
Histopathology: Early lesions → inflammation Late lesions → fibrosis and atrophy (NO Amyloid) Beta-cells mass → markedly reduced	**Histopathology:** Early lesions → nothing detectable Late lesions → Fibrosis and **Amyloid** Beta-cells mass → normal/slightly reduced
↓ insulin level insulin supplements are required	↑ or normal insulin level 1st, they try lifestyle modification, diet and exercise. Then, oral drugs & insulin supplements often needed

Other Forms:

Gestational Diabetes	Secondary Diabetes	Maturity Onset Diabetes of the Young
Develops in a few percent of pregnant women, due to: *insulin resistance of pregnancy* (combined with) *a B-cell defect.* Almost always abates (ends) following parturition.	It occurs secondary to: - other endocrine conditions (e.g. Cushing's syndrome) - or drug therapy (e.g. during treatment with glucocorticoids).	MODY: a rare autosomal dominant form of *inherited diabetes.* Associated with: Various gene defects affecting B-cells, like: - Glucokinase (an important sensor for glucose metabolism) - Several mutations in genes controlling development and function of the B-cells. Mutations in these genes, however, are not typically present in DM type 2.

Diagnositic Criteria:

Pateint having ***Polyuria*** or ***polydipsia***??

We do GTT(Glucose Tolerance Test) **which includes:**

- **FPG**(Fasting Plasma Glucose)
  - **Normal:** < **100 mg/dl**
  - **Diabetes:** ≥ **126 mg/dl**
- **PPG**(Post-Prandial Glucose in 2 hours)
  - **Normal:** < **140mg/dl**
  - **Impaired Glucose Tolerance:** = **140-199 mg/dl**
  - **Diabetes** ≥ **200 mg/dl**

"Impaired Fasting Glucose" need to be followed closely because they are at high risk of developing diabetes over time.

Diabetes Mellitus Type I:

Autoimmune destruction of the B-cells of the *islets of langerhands* in the pancreas. Characterized by:

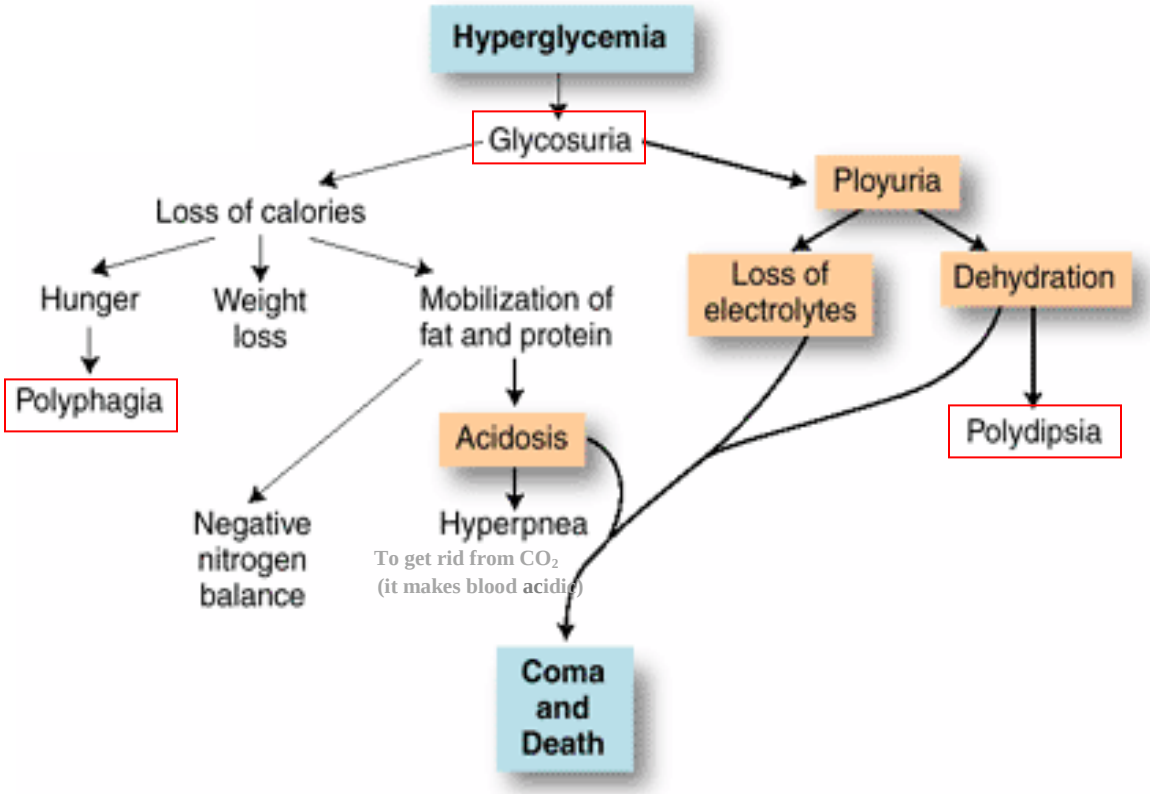
- Few/none functional B-cells in *islets of langerhans*.
- Extremely limited/nonexistent insulin secretion.

And this results in:

1- Body fat – rather than glucose – is metabolized as a source of energy → oxidation of fat → production of ***ketone bodies*** (acetoacetic acid and B-hydroxybutyric acid) → **metabolic ketoacidosis.**

2- Unsuppressed hepatic glucose output (glycogenolysis & gluconeogenesis) & ↓ glucose disposal in *Skeletal muscle* and *Adipose tissue* → ***Hyperglycemia*** → ***Glucosuria*** → loss of body water into urine → **dehydration**

Lead to coma and death



Epidemiology:

Ethnic groups:

Most common among:
Northern Europeans

Less common among:
Asians, African-Americans or Native-Americans.

Age Groups:

Most common onset:
at *Puberty*

Less common onset
at *elderly*
(with autoimmune destruction occurring over the years)

Time of the year:

Increased inceidence in
late-fall or *early-winter*

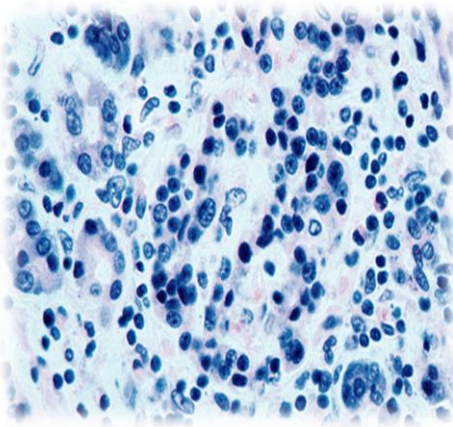
Pathogenesis:

1.GENETIC FACTORS

- **Major Histocompatibility Antigens called:**
  Human leukocyte **antigen** ***HLA-DR3*** or ***HLA-DR4***, or both in 95% of patients. **<< in immunology it's HLA-DQ !!**
- **The principal susceptibility *locus*[(1)] for it, is in the region encoding:**
  The class II MHC molecules on chromosome 6p21 (HLA-D)
- The children of ***fathers withT1DM*** are three times more likely to develop the disease than are children of ***diabetic mothers.***

(1): **a** locus **(plural** loci**) is the specific location of a gene** or **DNA sequence** on a **chromosome.**

2.AUTOIMMUNITY



- Cell mediated immune (CMI) mechanisms only present in type 1 DM with:
  Antibodies: Islet Cell Antibodyes (ICA)
  Antigens: islet antigens toward:
  - Components of B-cells - Insulin itself.
- Onset is gradual
  [antibodies appear years/months before clinical symptoms of insufficient insulin start to appear].
- This results in **Insulitis:**
  - ***Infiltrate of mononuclear cells in & around the islets of langerhans*.**
  - **Cytokines** (e.g. IL-1, IL-6, IF-α and intric oxide) resuling in →B-cell injury (slowly over the years)
- ***CD8+T lymphocytes pre-dominate***, although some CD4+cells are also present.
  ((normally, CD8 < CD4 but in this type of CMI, CD8 are the predominating T-cells))

Pathophysology of autoimmunity:

Damaged **islet cells** release antigens → Initial **activation of T cells** in the peripancreatic lymph nodes → **they cause β cell injury** → **TH1 cells secrete cytokines, including: IFN-γ and TNF & CD8+ CTLs directly kill β cells**

1- **T lymphocytes react against β-cell antigens and cause cell damage**.
(These T cells include CD4+ T cells of the TH1, which cause tissue injury by activating macrophages, and CD8+ cytotoxic T lymphocytes, which directly kill β cells and also secrete cytokines that activate macrophages).
→ Pancreatic lesions examined at the early active stages of the disease show cellular necrosis and lymphocytic infiltration. This lesion is called insulitis.

2- Locally produced cytokines damage β cells e.g. IFN-γ, TNF and interleukin-1

3- Autoantibodies against a variety of β-cell antigens, including:
insulin and **glutamic acid decarboxylase**,
are also detected in the blood of 70% to 80% of patients and may contribute to islet cell damage

3.ENVIROMENTAL FACTORS

Geographical and seasonal differences in the incidence of T1DM further suggest that environmental factors are ***important*** in its pathogenesis Such as:

Viruses and chemicals of:

- **Mumps**
- Group B **Coxsackie** viruses
- **Rubella** viruses.

Morphology

Early active stage:

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

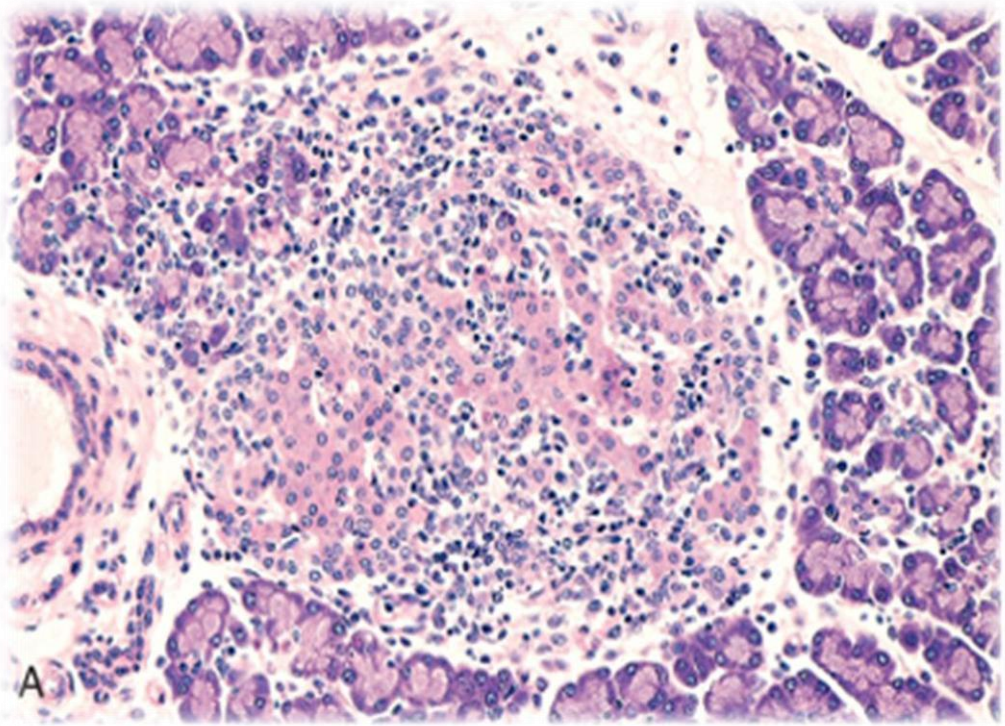
Chronic stage:

The islets are progressively depleted of Beta cells

The exocrine pancreas in chronic T1DM: often exhibits:

- Diffuse interlobular and interacinar fibrosis
- **Atrophy** of the acinar cells

- **Fibrosis of the islets is uncommon**
- **NO** deposition of **amyloid** in the islets of Langerhans, in contrast to T2DM



Diabetes Mellitus Type II

Epidemiology:

Almost 10% of persons older than 65 years of age are affected
[The disease usually develops in adults]

80% of patients with T2DM are overweight [obese].
It has been appearing in increasing numbers in younger age.

Pathogenesis: **mainly due to the following 2:**

1-Insulin resistance [Decreased ability of target cells to respond to insulin]

2-Inadequate (impaired) insulin secretion in response to glucose stimulation [B-cells dysfunction]

- **[B-cells dysfunction]**

Inability to secrete insulin when glucose is high.
This functional abnormality **is specific for glucose**, since the B-cells responds to other stimulants, such as amino acids.

Other Causes: B-cell function may also be affected by:
Chronically Elevated Plasma Levels of Free Fatty Acids that occur in ***obese persons.***

****This describes the relationship between the obesity and the insulin resistance and/or impaired insulin production****

- **[Genetic factors] → Multi-factorial**

The inheritance pattern is **complex** and thought to be due to multiple interacting susceptibility genes**.**

High Familial Predominance
- Among ***monozygotic twins***, both are almost always affected.
- **60%** of patients have either a parent or a sibling with the disease.

No association with **genes** of the major histocompatibility complex (MHC)

Lifestyle predominance
Obesity
Hypertension
Amount of exercise
↓
Influence the phenotypic expression of the disorder

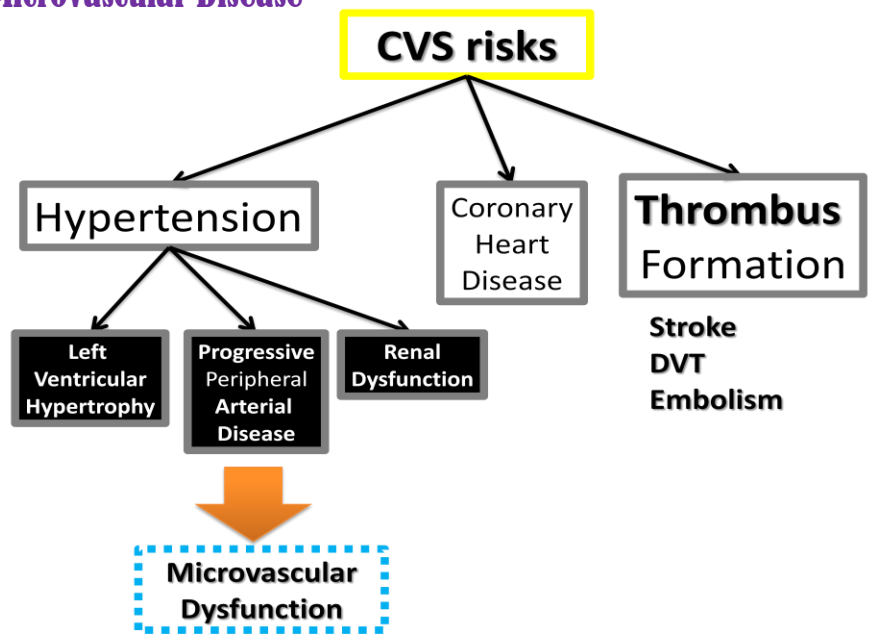
Histopathology:

B-cells are spared (no reduction or any morphologic lesion in them), but in the islets:

1- **Fibrous tissue** accumulates → may obliterate.
2- **Amyloid** deposits (especially in elderly patients).

Diabetes Complications:

1. Diabetic Microvascular Disease



2. Diabetic Nephropathy

1/3rd of renal failure cases, affecting both **T1DM (30-40% of them)** & **T2DM (20% of them).**

Occurrence depends on:

the ***Severity*** and the ***Duration*** of **Hyperglycemia**.

Glomeruli exhibit a <u>unique lesion</u> called:

Kimmelstiel-Wilson disease or **Nodular Gomerulosclerosis**

3. Diabetic Retinopathy

Risk is **higher in T1DM** (just like neuropathy).

30% Of T1DM patients with 20 years duration become **<u>Legally blind</u>**

4. Diabetic Neuropathy

Pain & abnormal sensation in the Extremeties.

Most common complication.

Related to "Microvasculopathy" involving small blood vessels of nerves (low supply)

Affects: Peripheral Sensory impairment (lead to foot ulcers)

Autonomic Nerve Dysfunction

With abnormalities in the ***Axons*** and the ***Myelin sheath*** and ***schwann cells.***

5. Infections:

Bacterial & Fungal occur in diabetic hyperglycemia if poorly controlled

- Bladder infection → Renal papillary necrosis (complication)
- **<u>Mucormycosis</u>:** a dangerous fungal infection.
  originates in ***Nasopharynx*** or ***Paranasal sinuses*** → **spreads rapidly** to the orbit and brain

<u>Gestational Diabetes:</u>

Diabetes occurring during pregnancy as ***Pregnancy is a state of insulin-resistance***. This can put both mother & fetus at risk.

- Among the females suffering from it during pregnancy, a small percentage may continue having it even after parturition.
- On the other hand, other percentages are highly susceptible to get T2DM (to get insulin resistance) later in life.