PATHOLOGY TEAM

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RED: Important infos. | Orange box: for the extra infos. in the comments of lecturer slids and talks | Blue box: for the infos. quoted from Robbins.

Introduction:

- Sir William Osler defined diabetes mellitus as “a syndrome due to a disturbance in carbohydrate e metabolism from various causes, in which sugar appears in the urine, associated with thirst, polyuria, wasting and imperfect oxidation of fats.”
- Major health problem that affects increasing numbers of persons in the developed world.
- Two major forms of diabetes mellitus are recognized, distinguished by their underlying pathophysiology.

*GLUCAGON IS THE COUNTER-REGULATORY HORMONE TO INSULIN.
*BRAIN IS INSULIN-INDEPENDENT .
*IN MUSCLE CELLS ,GLUCOSE IS EITHER STORED AS GLUCAGON OR OXIDIZED TO GENERATE ATP.
*IN ADIPOSE TISSUE , GLUCOSE IS PRIMARILY STORED AS LIPID.

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Diabetes Usually before 20 (childhood and puberty).	Diabetes Usually after 30
Abrupt; symptomatic (polyuria, polydipsia, dehydration); often sever with ketoacidosis.	Gradual; usually subtle.
Normal weight; recent weight loss is common.	Overweight.
Genetics predisposition <20% (moderate).	Genetics predisposition >60% (very strong).
Monozygotic Twins 50% concordant.	Monozygotic Twins 90% concordant.
HLA Association, antibodies to islet cell antigens +	No association.
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.

Management:

- Type 1:Insulin absolutely required.*insulin is provided as an injection or pumps.
- Type 2: lifestyle modification; diet, exercise, oral drugs, often insulin supplement needed.

T1DM (type 1 diabetes mellitus):

- Type 1 diabetes mellitus (T1DM), formerly known as insulin-dependent (IDDM) or juvenile-onset diabetes, is caused by autoimmune destruction of the insulin-producing B-cells in the pancreatic islets of Langerhans, and affects less than 10% of all patients with diabetes.

Type 2 DM (type 2 diabetes mellitus):

- Type 2 diabetes mellitus, formerly known as non–insulin-dependent(NIDDM)or maturity-onset diabetes, is 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.
  *in long-standing type 2 DM there is Amyloid AA deposition.

Other forms of diabetes mellitus:

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

Woman with gestational diabetes is at increased risk of developing diabetes later.& newborns from a mother which had gestational diabetes ,they usually born large.

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.
- Mutations in these genes, however, do not account for the typical prevalent forms of T2DM.

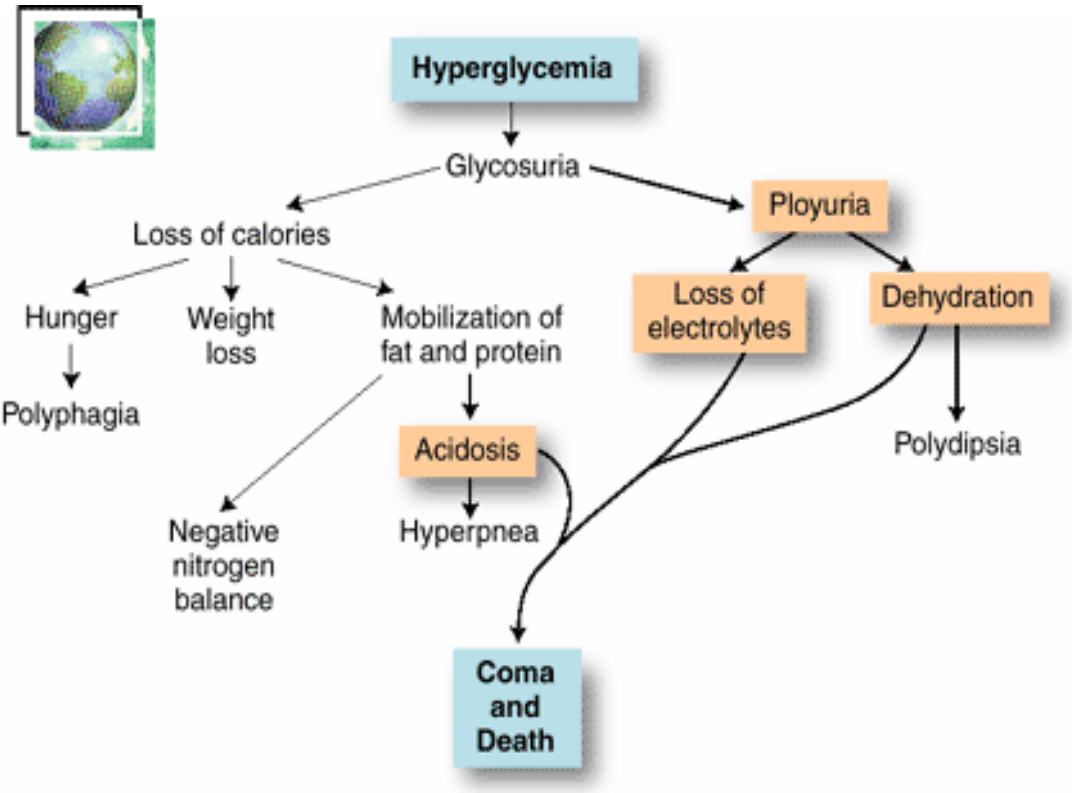
Criteria for Diagnosis:

- Fasting plasma glucose level of at least 126 mg/dL or a glucose level above 200 mg/dL taken anytime of day in a patient who typically experienced overt symptoms of polyuria and polydipsia.
- A normal fasting plasma glucose level is currently defined as <100 mg/dL.

- Patients with fasting glucose levels of 100 to 125 mg/dL are considered to have "impaired fasting glucose," and need to be followed closely because they are at high risk of developing diabetes over time.

Type 1 Diabetes Mellitus:

- Autoimmune destruction of the B cells in the islets of Langerhans.
- The disease is characterized by:
- Few if any functional B cells in the islets of Langerhans and
- 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.
- If uncorrected, the progressive acidosis and dehydration ultimately lead to coma and death



Type 1 diabetes most commonly develops in childhood, becomes manifest at puberty , and is progressive with age. Most individuals with T1DM depends on exogenous insulin supplementation for survival and without insulin ,they develop serious metabolic complications such as acute ketoacidosis and coma.

Epidemiology of type 1 diabete mellitus:

- 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 of T1DM:

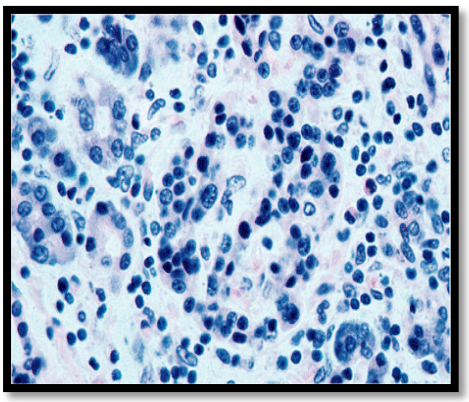
1-GENETIC FACTORS:

- Fewer than 20% of those with T1DM have a parent or sibling with the disease.
- Monozygotic twins : 50% concordant
- Environmental factors contribute in a major way to the development of the disease.
- However, certain genetic factors are important, especially major histocompatibility antigens.
- Some 95% of patients with type T1DM have either human leukocyte antigen (HLA)-DR3 or HLA-DR4, or both, compared with 20% of the general population.
- Susceptibility to T1DM is associated with the DQ locus.
- The children of fathers' withT1DM are three times more likely to develop the disease than are children of diabetic mothers.

2- 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.

Insulitis →



Autoimmunity of type 1 diabetes mellitus:

- 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.
- 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.

3- ENVIRONMENTAL FACTORS:

- Viruses and chemicals, 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.

Pathology:

- Lymphocytic infiltrate in the islets (insulitis), sometimes accompanied by a few macrophages and neutrophils
- As the disease becomes chronic, the B cells of the islets are progressively depleted of Beta cells.
- Fibrosis of the islets is uncommon. (it's more with T2DM)
- 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.

Morphology:" those following changes are more commonly with T1DM than T2DM":
-Reduction in the number and size of islets.
-leukocytic infiltration of the islets (insulitis) .
-An increase in the number and size of islets is especially characteristic of nondiabetic newborns of diabetic mothers.
Go to page 781 in robbins " morphology box"

Questions:

1- most common histological characteristic of T2DM in the pancreas is :

A-calcification
B-Amyloid AA deposition
C-eosinophilic infiltrate

2-what is the most serious complication of T1DM:

A-retinopathy
B- heart failure
C- Acute ketoacidosis

Answers :
1- B
2- C

Best wishes <3