DM 1

Objectives:
***not given**

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Resources: 435 team + Davidson + kumar + Recall questions step up to medicine + 436 Pharmacology team endocrine block.

- Editing file
- Feedback

The doctor didn't give us his slides so it's based on 435+davidson & notes

Introduction

What is DM1 ?

- ➔ Diabetes mellitus is a clinical syndrome characterised by an **increase in plasma blood glucose** (hyperglycemia)
- ➔ Type 1 DM is characterized by a severe deficiency of insulin. T cell-mediated autoimmune disease
- ➔ In diabetes mellitus, it's not about the disease itself , it's about the complications it causes.
- ➔ If we screen 10,000 child for DM1 , we will get 30 positive cases in Saudi Arabia.
- ➔ Type 1 DM is a **genetic disease not a familial disease.**
- ➔ DM1 is Not related to obesity
- ➔ In KSA we have two peaks of incidence, at age 9 and age 13.
- ➔ most common in young but can occur in any age (last week the doctor diagnosed a 54 y/o patient)
- ➔ 7th leading cause of death in KSA
- ➔ DM1 usually associated with other autoimmune diseases, so we have to look for them. including thyroid disease, coeliac disease, Addison's disease, pernicious anaemia and vitiligo

What is the difference between a genetic disease and a familial disease?

- ➔ **Genetic Disease**: a single gene responsible for a pathology. (e.g. Diabetes Mellitus 1).
- ➔ **Familial Disease**: a collection of genes (Polygenic) from a previous generation passed to another generation (Hereditary) (e.g. Diabetes Mellitus 2).
- ➔ DM1 results from genetic + environmental + immune

***if you were asked which type is more familial? it will be Type 2 not 1!!!! However both can be familial.**

clinical features of the two main forms of diabetes:

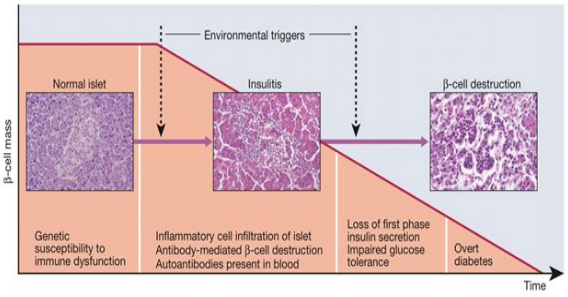
Table 20.2 The spectrum of diabetes: a comparison of type 1 and type 2 diabetes mellitus

	Type 1	Type 2
Age	Younger (usually <30)	Older (usually >30)
Weight	Lean	Overweight
Symptom duration	Weeks	Months/years
Higher risk ethnicity	Northern European	Asian, African, Polynesian and American-Indian
Seasonal onset	Yes	No
Heredity	HLA-DR3 or DR4 in >90%	No HLA links
Pathogenesis	Autoimmune disease	No immune disturbance
Ketonuria	Yes	No
Clinical	Insulin deficiency ± ketoacidosis Always need insulin	Partial insulin deficiency initially ± hyperosmolar state Need insulin when beta cells fail over time
Biochemical	C-peptide disappears	C-peptide persists

Pathogenesis:

1) Autoimmune:

How is DM 1 a genetic disease ?



- ➔ On **chromosome 6, short arm, segment DR3 and 4** (a gene complex) will drive the mRNA to make something called Islet cell antibodies (ICA), these antibodies will go through the blood circulation to reach the pancreas where they attack and cause an inflammation **(Insulitis) & destruction of Beta cells** thus causing insulin deficiency (hypoinsulinemia).
- ➔ Among 13 persons who have DR3 and 4, only one gets the disease.

*The pathology in the pre-diabetic pancreas is characterised by 'insulitis'

2) Environmental:

- ➔ An infection with mumps virus, coxsackie B virus or EBV will trigger B lymphocytes to produce antibodies (to fight the viral infection off), so as the mRNA starts transcripting antibodies against the virus it will also activate segment DR3 and 4 which will produce the **Islet cell antibodies (ICA).**

Clinical Presentation:

Acute presentation:

- ➔ The main symptoms: polyphagia, polydipsia , polyuria and weight loss .polydipsia , polyuria will happen when the glucose is over 200
- ➔ Ketonuria
- ➔ **Onset:** typically in youth (before age 20).
- ➔ Symptoms often develop quickly over days to weeks. "Acute" . Sometimes appear after an illness.

Subacute presentation:

- ➔ lack of energy, visual blurring.
- ➔ pruritus vulvae or balanitis that is due to Candida infection

presentation as complications:

- ➔ Staphylococcal skin infections
- ➔ Retinopathy
- ➔ polyneuropathy
- ➔ Erectile dysfunction
- ➔ Arterial disease,
- ➔ peripheral gangrene.
- ➔ Patients often present with acute **DKA (most common presentation)**
- ➔ DM 1 is in younger age, it is immunological, it is acute and it involves DKA.

TABLE 4-5 Symptoms of Diabetes Mellitus

Symptom	Cause
Polyuria	Glucose in renal tubule causes osmotic retention of water, causing a diuresis
Polydipsia	A physiologic response to diuresis to maintain plasma volume
Fatigue	Mechanism unknown, but probably due to increased glucose in plasma
Weight loss	Due to loss of anabolic effects of insulin
Blurred vision	Swelling of lens due to osmosis (caused by increased glucose)
Fungal infections	Fungal infections of mouth and vagina common—*Candida albicans* thrives under increased glucose conditions
Numbness, tingling of hands and feet	Neuropathy Mononeuropathy: due to microscopic vasculitis leading to axonal ischemia Polyneuropathy: etiology is probably multifactorial

Signs and symptoms of DKA: (will be discussed in "Complications of diabetes lecture")

- ➔ Polyuria, Polydipsia
- ➔ Abdominal pain ± Nausea, vomiting
- ➔ Dehydration (depletion of 6L, depletion
- ➔ Fruity breath
- ➔ Kussmaul breathing "air hunger"
- ➔ Mental changes (confusion, coma)
- ➔ weight loss (insulin has anabolic effect so lack of it in DM1 will cause weight loss)

Diagnosis:

Sensitivity & specificity:

- ★ A sensitive test for screening, when it is positive that means you might have the disease. When it is negative that means for sure you are normal.
- ★ A specific test is for diagnosis, when it is positive that means the disease is present. When it is negative that means you might be normal.

diabetes tests			
Test	SENSITIVITY	SPECIFICITY	diagnostic values
Fasting blood sugar	-	+	>=126 mg/dL (7 mmol/L)
Random Blood Sugar	+	-	> 200 mg/dl (11.1 mmol/l)
OGTT (oral glucose tolerance test)	+	+	-
Hb1Ac	+	-	>=6.5%

- Random Blood Sugar → sensitive test → good for screening → when negative, rule out the disease.
- Fasting blood sugar → specific test → good for diagnosis → when positive, the disease is present.
- OGTT (oral glucose tolerance test) → sensitive & specific so it is the **best confirmatory test.** (but it is expensive & time consuming).

Box 20.1 WHO diagnostic criteria

WHO criteria for the diagnosis of diabetes are:

- Fasting plasma glucose >7.0 mmol/L (126 mg/dL)
- Random plasma glucose >11.1 mmol/L (200 mg/dL)
- One abnormal laboratory value is diagnostic in symptomatic individuals; two values are needed in asymptomatic people. The glucose tolerance test is only required for borderline cases and for diagnosis of gestational diabetes.
- HbA_{1c} >6.5 (48 mmol/mol)

The glucose tolerance test – WHO criteria

	Normal	Impaired glucose tolerance	Diabetes mellitus
Fasting	<7.0 mmol/L	<7.0 mmol/L	>7.0 mmol/L
2 h after glucose	<7.8 mmol/L	7.8–11.0 mmol/L	>11.1 mmol/L

- Adult: 75 g glucose in 300 mL water
- Child: 1.75 g glucose/kg bodyweight
- Only a fasting and a 120-min sample are needed
- Results are for venous plasma – whole blood values are lower.

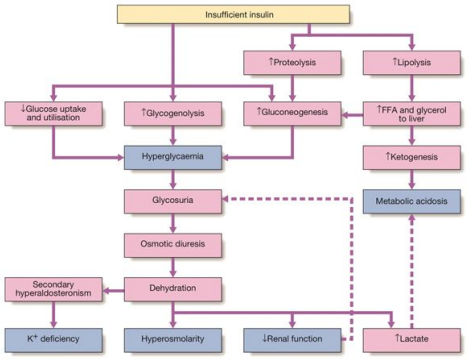
Note: There is no such thing as mild diabetes. All patients who meet the criteria for diabetes are liable to disabling long-term complications.

Management

1) Insulin

Rationale:

- ➔ Insulin is the main treatment and cornerstone of type 1 management.
- ➔ Type 1 diabetics start out deficient of insulin (the disease actually isn't evident until **90%** of functional beta cells are lost) that's why we start them immediately on insulin. (unlike type 2)



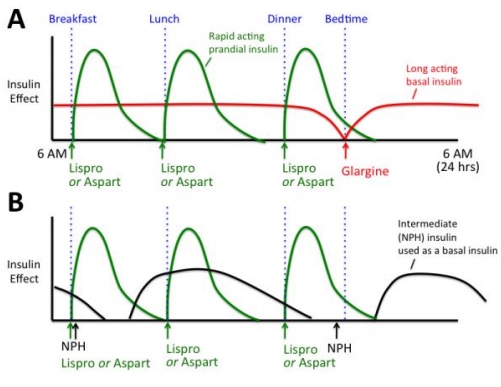
Method of administration:

- ➔ Self-administered by SC injection in abdomen, buttocks, arm,leg.
- ➔ Given intravenously or IM for emergency **ketoacidosis**.

Why not orally?

The human insulin is a dimer of an A-chain and B-chain,which are linked together by disulfide bonds. if you take orally stomach acid will break it down and **inactivate it.**

Insulin preparations			
Ultra short acting insulins	Short acting insulins	Intermediate acting insulin	Long acting insulin
Lispro, Aspart	Regular, Humulin	NPH, Lente	Glargine, Detemir



Insulin side effect:

•Hypoglycemia
• Hypersensitivity reactions
• Lipodystrophy at injection site
• Weight gain (due to anabolic effects of insulin)
• Insulin resistance.
• Hypokalemia "cuz insulin causes the K uptake into the cells"

2) Diet & lifestyle modifications:

Rationale:

- ➔ Like type 2 patients people with type 1 will need diet and exercise to improve their chances against complications.
- ➔ Similar modifications to type 2 patients.

3) Beta cells transplantation

Types:

- ➔ A- Beta cells transplant: it is very effective way of treatment and can **cure** patient but it has some problems
  - ◆ For each patient we need pancreas of 2 brain dead individuals.
  - ◆ The transplant will start to dysfunction after 5 years.
  - ◆ The patient need to be on immunosuppressant.
- ➔ Whole pancreas transplantation is carried out in a small number of patients with diabetes each year.
- ➔ At present, the procedure is usually undertaken only in patients with end-stage renal failure who require a combined pancreas/kidney transplantation and in whom diabetes control is particularly difficult, e.g. because of recurrent hypoglycemia.

*Note that long term immunosuppression therapy should be carried out

Summary

- DM1: Diabetes mellitus is a clinical syndrome characterized by an increase in plasma blood glucose (hyperglycemia) with severe deficiency of insulin (hypoinsulinemia(, genetic disease not a familial disease ، Not related to obesity.
- Type 1 diabetics start out deficient of insulin (the disease actually isn't evident until 90% of functional beta cells are lost) .

Pathogenesis:- 1st Autoimmune :- DR3 and DR4 drive > mRNA > make islet cell antibodies (ICA) > Destruction beta cell > hypoinsulinemia

2nd Environmental :- mumps virus or coxsackie B virus trigger > B lymphocytes to produce antibodies > stimulate DR3 and DR4 > form ICA > Destruction beta cell (hypoinsulinemia) .

- Clinical Presentation: The main symptoms: polyphagia, polydipsia , polyuria and weight loss.
- Signs : Kussmaul breathing , Fruity breath

Diagnosis :- Sensitive :- 1- Hb1Ac 2- Random Blood Sugar

Specific :- 1-OGTT (oral glucose tolerance test) → sensitive & specific so it is the best confirmatory test

2- Fasting blood sugar specific only

Treatment : 1-Insulin 2-Diet 3-transplantation

Questions

1. The most common breathing pattern in DKA?

A. Sighing breathing.

B. Obstructed breathing.

C. Kussmaul breathing.

2. What is the most common adverse event of insulin in type 1 diabetes?

A. Hypoglycemia.

B. Lipohypertrophy.

C. Skin allergy.

3. What is the best confirmatory test of DM1?

A. Fasting blood sugar.

B. Oral glucose tolerance test.

C. Hb1Ac.

4. The most common presentation of DM1?

A. Vision disturbances.

B. DKA.

C. Numbness.

5. The cornerstone of type 1 diabetes management is?

a. Beta cell transplant.

b. Metformin.

c.Insulin.

Answers:

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