Diabetes Mellitus 1

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Objectives:

- **Not given yet**

References:
Doctor's notes - Red
Step up / davidson - Black
Extra explanation - Grey

Optional:

Editing file

Chapter 21

DM 1&2 and DKA
17:47

❖ Introduction :

- **Diabetes mellitus is a clinical syndrome characterised by an increase in plasma blood glucose (hyperglycaemia)**
- **In DM , it's not about the disease itself , it's about the complications of it.**
- **If we screen for type 1 DM in 100000 , the prevalence will be 30 children got type 1 DM in Saudi Arabia.**
- **Type 1 DM is characterized by a severe deficiency of insulin. Patients require insulin to live.**
- **DM1 is Not related to obesity.**
- **Type 1 DM is a genetic disease not a familial disease .**

Genetic disease: one gene is responsible [Type 1 DM]
Familial disease: More than one gene (Polygenic) are responsible [Type 2 DM]

❖ Genteics :

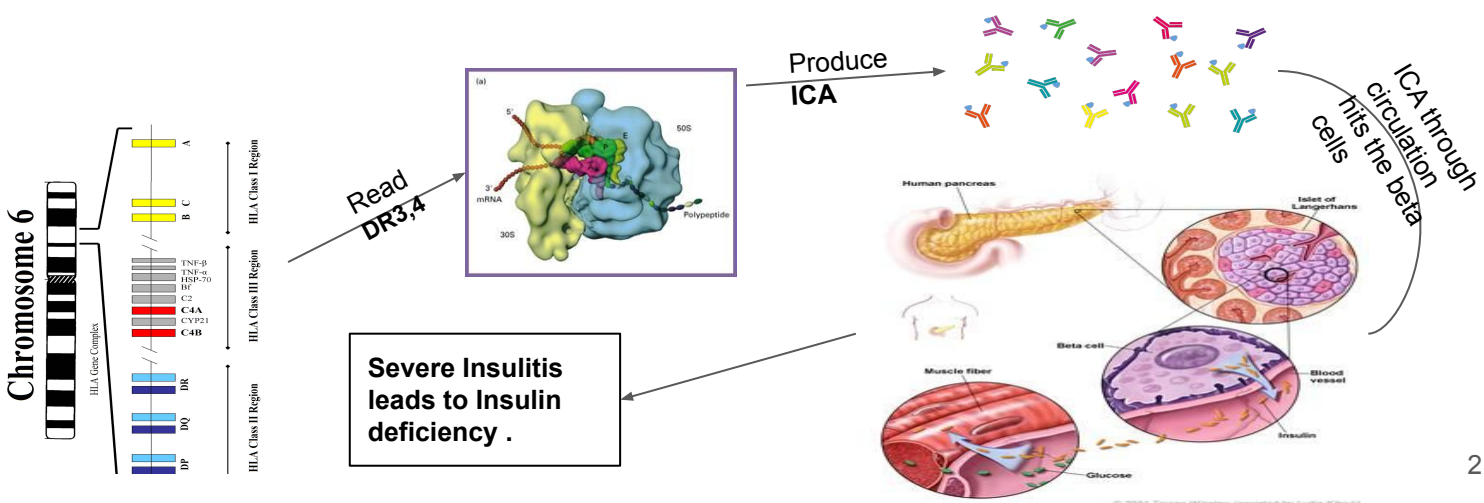
At the beginning we should understand the type of genes :

- Genetic Disease : Is a single gene responsible for a pathology .
- Familial Disease : Is a collection of genes (Polygenic) from previous generation (Family) passed to another generation (Heredity) .
- Type Ⅱ is more FAMILIAL than type Ⅰ.
- Familial is more inheritance than genetic .

If an identical twin one of them had DM type Ⅱ = The other one 100% will be affected.

If an identical twin one of them had DM type Ⅰ = The other one 50% will be affected.

So Type 1 DM is a genetic disease , how ?
It is located on chromosome 6 , short arm , segment DR3,4
(When this segment mRNA read the DR3,4 segment it will translated to ICA (Islet cell antibodies) , these ICA will go through the blood circulation, reaches the pancreas, destructs the BETA cells and causes Insulitis which lead to severe insulinopenia).



❖ Pathogenesis:

- **Autoimmune disease : (Explained in the previous slide).**
- **Environmental: an infection with mumps virus or coxsackie B virus this will trigger for B lymphocytes to produce antibodies so when the m-RNA is reading to produce antibodies against the virus it will also stimulate the lower or upper segments to produce antibodies so produced ICA .**

! **Sign and symptoms of DKA:**

- **Polyuria, Polydipsia**
- **Abdominal pain ± Nausea, vomiting**
- **Dehydration**
- **Fruity breath**
- **Kussmaul breathing**
- **Mental changes (Ex: confusion, coma)**

❖ Clinical Presentations:

- **Cardinal symptoms are (polyphagia, polydipsia , polyuria and weight loss).**
- **Onset typically in youth (before age 20).** Although, It can happen at any age
- **Symptoms often develop quickly over days to weeks.** "Acute"
- **Sometimes appear after an illness.**
- **Patients often present with acute DKA(Metabolic Acidosis).** Acetone high acidity: a high concentration of ketone bodies is usually accompanied by insulin deficiency, hyperglycemia, and dehydration. Particularly in type 1 diabetics the lack of insulin in the bloodstream prevents glucose absorption, thereby inhibiting the production of oxaloacetate (a crucial molecule for processing Acetyl-CoA, the product of beta-oxidation of fatty acids, in the Krebs cycle) through reduced levels of pyruvate (a byproduct of glycolysis), and can cause unchecked ketone body production (through fatty acid metabolism) potentially leading to dangerous glucose and ketone levels in the blood due to unabling to excrete them through the kidneys . More details in the next lecture "complications of DM" Focus on it.
- **Bottom line: In DM1, since there is severe insulin deficiency there will be a shifting of metabolism from Glucose metabolism (glycolysis) toward fatty acid metabolism which lead to production, accumulation and building up of ketone bodies resulting in diabetic ketoacidosis(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

❖ Diagnostic Tests :

- **Two fasting blood glucose measurements greater than 126 mg/dL.**
- **Single glucose level(Random) above 200 mg/dL with above symptoms.**
- **Increased glucose level on oral glucose tolerance testing.** 2 hour (Glucose Tolerance Test) with 75g intake, a glucose level below 7.8 mmol/L (140 mg/dL) is normal
- **Hemoglobin A1c (Glycated Hemoglobin) >6.5% is a diagnostic criterion and is the best test to follow response to therapy over the last several months.**

DM type Ⅱ once diagnosed should be transferred to screen for the DM complications such as: Retinopathy, Neuropathy, Nephropathy , Cardiopathy; even if there are no symptoms . "usually Diagnosed late of the disease = more possibility of developing complications"

- DM type I send for screening of microvascular after 5 years of diagnosis, because they won't develop complications yet. "usually Diagnosed early of the disease = less possibility of developing complications"

❖ Specificity & Sensitivity of the tests:

- **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. Good to detect the disease.**
- **(Fasting blood sugar)**
- **Sensitive test : for screening , when it is positive that mean you might have the disease. When it is negative that mean for sure you are normal. Good to rule out the disease.**
- **(Random Blood Sugar)**
- **OGTT (oral glucose tolerance test) is the best confirmatory test but it is expensive .**

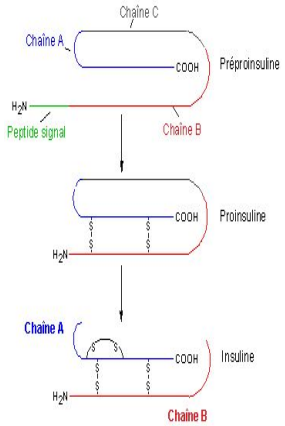
	SENSITIVITY	SPECIFICITY
FASTING BLOOD SUGAR	-	+
RANDOM BLOOD SUGAR	+	-
OGTT	+	+

- **HbA1c: Is used to get an overall picture of what the average blood sugar levels have been over a period of weeks/months**
- **The equivalent of HbA1c is Fructosamine (Glycated Albumin) both of them are useful tests but the life span of HbA1c is accompanied with RBC = 120 days, unlike Fructosamine = 3 weeks.**
- **So when do we use Fructosamine test ?**

In patients with diseases that reduce red blood cell lifespan, such as hemolytic anaemia or hemoglobinopathies such as sickle-cell disease, a hemoglobin-based A1c test can be misleadingly low. A1c results may also be falsely high or low in hemoglobinopathies because abnormal hemoglobin variants can interfere in the analysis. In these cases, fructosamine measurement can be used as a marker of blood sugar levels, as its measurements are based on albumin instead of hemoglobin. However, any condition that changes serum albumin (such as the nephrotic syndrome) will affect the fructosamine result.

❖ Management:

- **Insulin is the main treatment.**
- **The human insulin is a dimer of an A-chain and B-chain,which are linked together by disulfide bonds.**
- **The pro-insulin is linked to C-peptide,why? To be inactive and not consumed**
- **Method of administration:**
  - **Self-administered by SC injection in abdomen, buttocks, arm,leg.**
  - **Given intravenously for emergency ketoacidosis.**
- **Regimens:**
  - **Type I diabetic patients require 0.5 - 1.0 unit/kg per day to achieve acceptable glycemic control.**
  - **Start with a conservative dose and adjust the regimen according to the patient's glucose levels.**
  - **Many different regimens exist, and every patient has unique needs.**



- **Insulin preparations:**

★ **Ultra short acting insulins: (eg: Lispro, aspart).**

I. **very fast onset of action and short duration**
II. **Before meals**
III. **Can be used in emergency diabetic ketoacidosis as (I.V)**

★ **Short acting insulins: (eg: regular, humulin).**

I. **Same as natural insulin**
II. **Before meals**
III. **Can be used in emergency diabetic ketoacidosis as (I.V)**
IV. **Can be used in pregnancy**

★ **Intermediate acting insulin: (eg: NPH, lente).**

★ **Long acting insulin: (eg: glargine,detemir). It's the one given at evening and is a part of invasive insulin therapy**

- **Intensive insulin therapy:**
  - ***Long-acting insulin*: is given once daily in the evening.**
  - ***Regular insulin*: is given 30 to 45 minutes before each meal, and should be adjusted according to preprandial home glucose measurements.**
  - **These more aggressive therapies have been shown to significantly decrease the incidence of diabetes complications such as retinopathy and microalbuminuria when compared to prior regimens. All attempts should be made to get patients on more aggressive treatment protocols.**
  - **With intensive insulin therapy, the risk for hypoglycemia is a serious concern.**
  - **Alternatively, a continuous SC infusion of insulin can be given via an insulin pump. Preprandial boluses are given in addition to the basal infusion.**

! Monitoring Glucose levels in DM:

- **HbA1c gives an estimate of the degree of glucose control over 2 to 3 months**
- **The American Diabetes Association recommends a treatment goal of HbA1c <7.0%. In general, HbA1c >10% is poor control, 8.5% to 10% is fair control, 7.0% to 8.5% is good control, and <7.0 is ideal.**
- **The American Diabetes Association recommends keeping fasting blood glucose level <130 mg/dL and peak postprandial blood glucose <180 mg/dL**

Insulin preparation	Onset of action (minutes)	Peak action (hours)	Duration of action (hours)
Rapid acting			
Lispro/aspart/glulisine	15–30	1–2	3–6
Short acting			
Human regular	30–60	2–4	6–10
Intermediate acting			
Human NPH	60–150	4–8	10–20
Long acting			
Glargine	60–120	Flat	24

Source: Curr Med Res Opin © 2006 Librapharm Limited

Somogyi effect & Down phenomena

First of all, you must remember two things:
1- Everythings in our body is in balance process, and once that balance gets disturbed the problems will come. and this is the story between insulin & counterregulatory hormones
2- Normally in the morning, The following hormones get released to give you the power and the energy for your day:-

- **Growth hormone**
- **Cortisol**
- **Epinephrine**
- **Glucagon**

Also they known as "counterregulatory hormones of insulin" as they are released in response to decreased blood sugar level and in turn will cause increase in blood sugar level

in normal person these hormones get released in the morning,and it may cause morning hyperglycemia, right? fortunately Not, because in normal person insulin will take over and make a balance in blood sugar level

Suppose if there is no insulin OR deficient insulin "in case of DM" → Blood sugar will increase in the morning which gives rise to Morning hyperglycemia. This what's known for "Down phenomena"

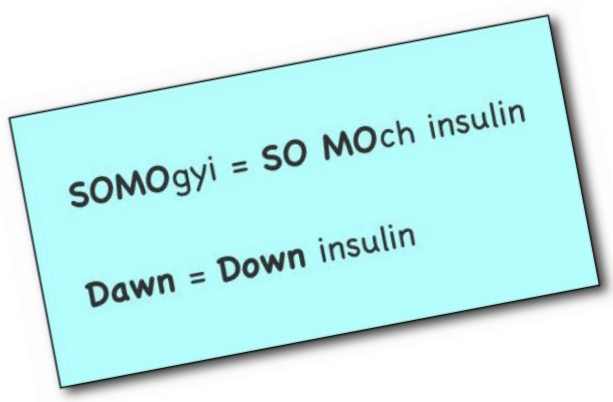
Moving to "Somogyi effect", it's also use the similar hormones and give rise to Morning hyperglycemia. However, the difference that in somogyi effect diabetic patient may induce nocturnal hypoglycemia due to taking evening insulin. As a result of this, the counterregulatory hormones will counteract and increase the blood sugar levels causing hyperglycemia in the morning.

Bottom line:

- **Somogyi effect & Down phenomena → Morning hyperglycemia**
- **Down phenomena occur when endogenous insulin secretion decrease**
- **Somogyi effect is present in the case of excessive amounts of exogenous insulin**
- **Somogyi effect is a rebound response to nocturnal hypoglycemia**

The purpose of All what we discussed is to say if there is a need in insulin dose adjustment
In case of:

- **Somogyi effect → Decrease the dose of insulin. To avoid nocturnal hypoglycemia**
- **Down phenomena → Increase the dose of insulin to give coverage of overnight hours. To make sure there won't be hyperglycemia in early morning**



❖ Then what about Beta cells transplantation ?

Beta cells transplant: it is very effective way of treatment and can cure patient but it has some problems:

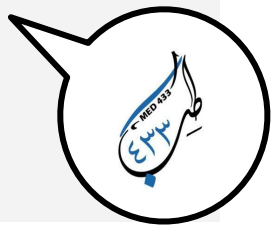
- **For each patient we need pancreas of 2 brain dead body.**
- **The transplant will start to dysfunction after 5 years.**
- **The patient need to be on immunosuppressant.**
- **Stem cells: is not effective yet because they cannot control the production of insulin**

Inpatient management of diabetic patients (sliding scale)

- An insulin sliding scale (SSI) of regular insulin doses given according to bed- side finger-stick glucose determinations is helpful in controlling blood glucose levels in the hospital setting.
- In general, SSI should be used in addition to a regimen of intermediate-acting insulin. If given alone, hyperglycemia usually results.
- Monitor blood glucose four times per day: before meals and at bedtime.
- If the home insulin dose is unclear, or if the patient anticipates greater requirements of insulin due to an illness, use the following approach to adjust appropriate insulin doses:
  1- Take the total number of units of regular insulin that the patient required in 1 day (while on the sliding scale).
  2-Add two-thirds of this to the pre breakfast dose and one-third before dinner. It should be given as 70/30 (i.e., 70% NPH/30% regular).

Modifying insulin doses

- Physical activity—depending on the intensity of the activity, decrease insulin dosage 1 to 2 units per 20 to 30 minutes of activity.
- During illness, administer all of the routine insulin. Many episodes of DKA occur during episodes of illness.
- Stress and changes in diet require dosing adjustments.
- Patients undergoing surgery should get one-third to one-half of the usual daily insulin requirement that day, with frequent monitoring and adjustments as necessary.



MCQ's

Q1:A 6-year-old girl presents to accident and emergency with severe abdominal pain, nausea and vomiting. On examination, the patient is tachypnoeic, capillary refill is 3 seconds and she has a dry tongue. While listening to the patient's lungs, you detect a sweet odour from her breath. The most likely diagnosis is:

A. Diabetic ketoacidosis
B. Non-ketotic hyperosmolar state
C. Gastroenteritis
D. Pancreatitis
E. Adrenal crisis

Q2:An 18-year-old Caucasian woman presents to her physician with complaints of excessive thirst over the past several months. Dipstick urinalysis demonstrates 4+ glucose in the urine. Blood chemistries demonstrate glucose of 420 mg/dL. In Caucasian patients, the condition affecting this woman is most strongly associated with which of the following HLA types?

(A) DR1 and DR2
(B) DR1 and DR3
(C) DR2 and DR3
(D) DR2 and DR4
(E) DR3 and DR4

Q3:A 22-year-old woman with type 1 diabetes presents to the emergency department with anorexia, nausea, vomiting, and abdominal pain. She is recovering from pneumonia and has had much difficulty regulating her blood sugars lately. On arrival to the emergency department, her blood glucose is 760 mg/dL, sodium is 125 mEq/L, potassium is 3.0 mEq/L, bicarbonate is 12 mEq/L, chloride is 92 mEq/L, and her blood is positive for ketones by acetone screening, lich of the following is the most appropriate initial step in management?

(A) Broad coverage antibiotic therapy
(B) IV glucose and insulin
(C) IV hypertonic saline
(D) IV potassium
(E) IV saline

Q4:A 7-year-old girl is brought to the emergency department by hei. parents with a complaint of severe polyuria and polydipsia, laboratory examination reveals ketones in her urine, which of the following is the most likely source of the ketones?

(A) Free fatty acid breakdown
(B) Gluconeogenesis
(C) Glycogenolysis
(D) Protein breakdown
(E) Triglyceride breakdown

Q5:A 52-year-old African-American woman with type 2 diabetes mellitus (DM) presents to her physician's office and states that she has been "feeling lousy in the morning." She notes that she reliably checks her blood glucose levels, and is frustrated at the fact that she often has a blood sugar level in the 120s at night, followed by a level in the 170s to 180s the following morning. The patient's primary care physician increased her nightly dose of neutral protamine Hagedorn insulin 1 month ago, but her morning glucose levels have only become more elevated.She has recently begun to limit her carbohydrate intake at night, with no effect. This patient's morning hyperglycemia might most likely be alleviated by which of the following?

(A) Decreasing neutral protamine Hagedorn insulin at night
(B) Increasing neutral protamine Hagedorn insulin at night
(C) Increasing neutral protamine Hagedorn insulin in the morning
(D) Increasing regular insulin at night
(E) Increasing regular insulin in the morning

^

Small question^^, according to this scenario, what do you think this patient has? Somogyi effect OR Down phenomena? Ans: is Somogyi effect

Answers: 1.A, 2.E, 3.E, 4.A, 5.A

Thank you

If you have any question please contact with us at:
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