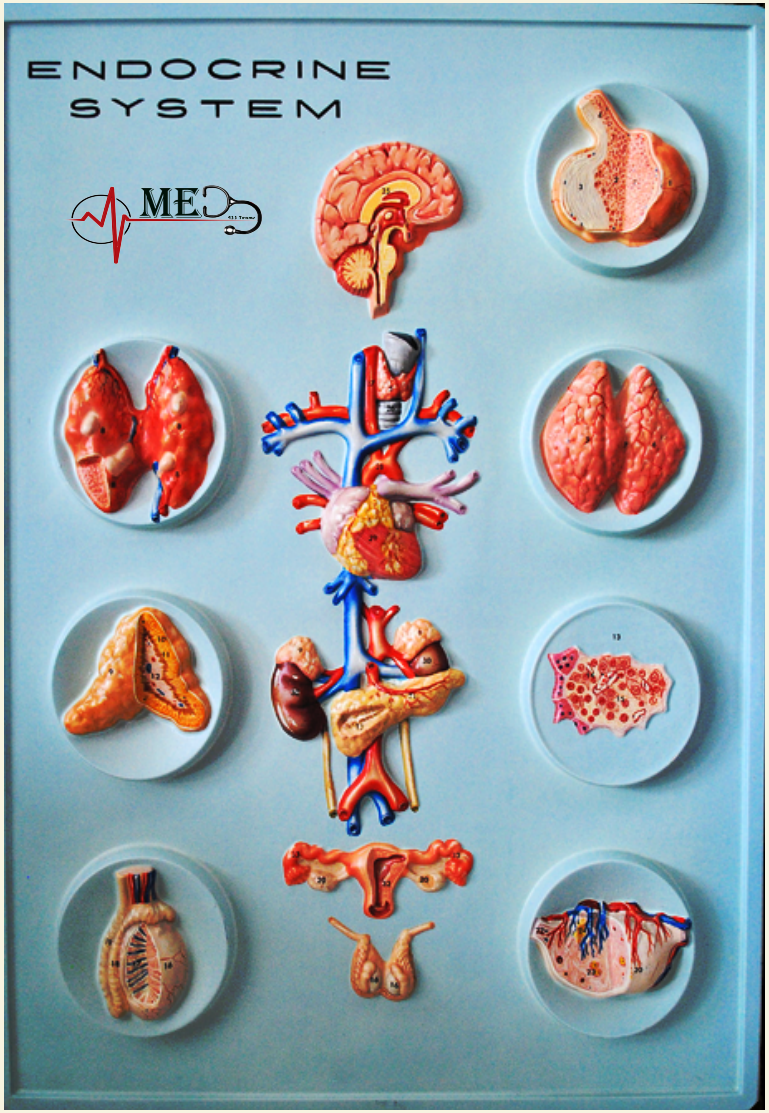


LECTURE 7 :

Metabolic changes in diabetes mellitus

Objectives:

- Background
- Diagnostic criteria for DM
- Metabolic changes in DM
- Mechanisms of diabetic complications

Abbreviations:

DM → diabetes mellitus
T1DM → type 1 diabetes mellitus
T2DM → type 2 diabetes mellitus
FPG → fasting plasma glucose
OGTT → oral glucose tolerance test
A1C → glycated hemoglobin
VEGF→ vascular endothelial growth factor

*** The reference ranges of the normal values will be given in exam**

Comparison of type 1 and type 2 DM

	Type 1	Type 2
Age of onset	Childhood	Adult
Symptoms develop	Rapidly	Gradually
Defect & deficiency	Beta cells are destroyed	Insulin resistance + inability of beta cells to produce enough insulin
ketosis	common	Rare
Plasma insulin	low	A-high early in disease B-low in disease of long duration
Acute complication	Ketoacidosis	Hyperosmolar coma
Genetic predisposition	Moderate	Very strong
Use of oral hypoglycemic	Unresponsive	Responsive
Treatment	Insulin is always necessary	Diet, exercise, oral hypoglycemic, +/- insulin

Natural course

Type 1 DM

1-exposure to a virus or toxin may start beta cell destruction =>

↓ Insulin production.

2-insulin secretory capacity falls below a threshold & the symptoms appears

Type 2 DM

1- Obese individuals develop insulin resistance which may precede the development of DM.

2- They show Compensatory hyperinsulinemia in early stages

3- β-cell dysfunction occur marked by ↓insulin and worsening hyperglycemia

1: Fasting is defined as no caloric intake for at least 8 hrs

Criteria for diagnosis of DM:

1- Categories of increased risk for diabetes

FPG[1]=5.6-6.9 mmol/l

OGTT=7.8-11 mmol/l

A1C= 5.7-6.4%

2- Diagnosis of diabetes

FPG > 7 mmol/l

OGTT > 11.1 mmol/l

A1C > 6.5%

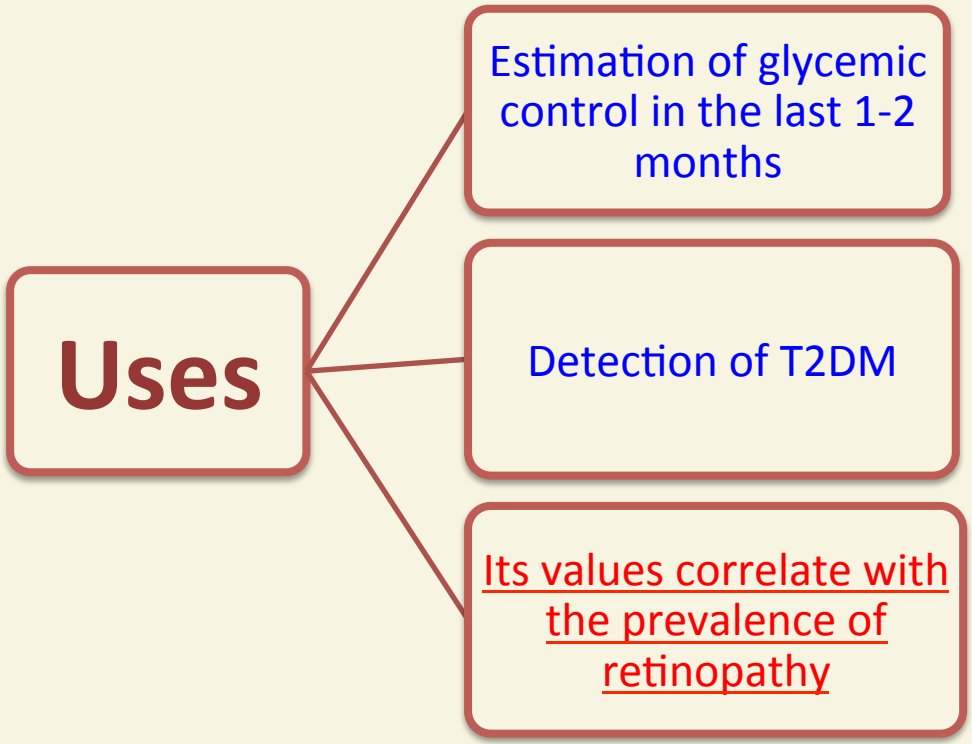
Random plasma glucose > 11.1 mmol/l

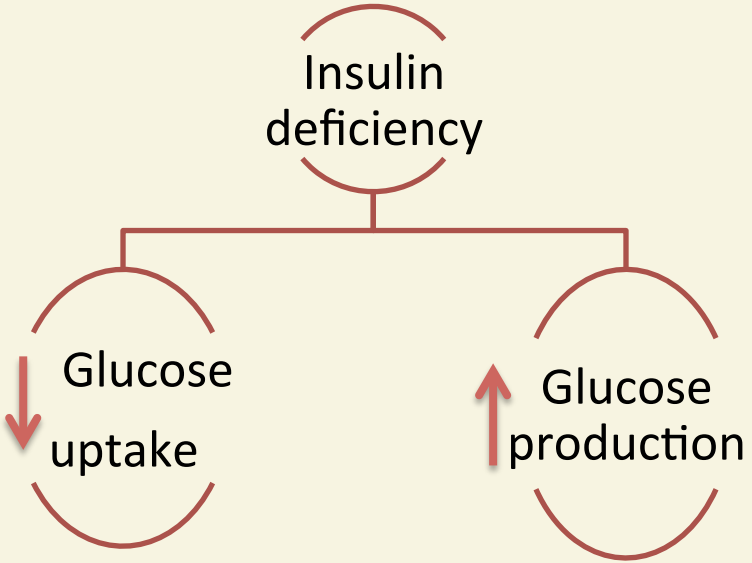
+ Hyperglycemia symptoms

Hemoglobin A1C:

- Is the result of non enzymatic covalent glycosylation of hemoglobin

- Assays for A1C has to be standardized according to the National Glycohemoglbin Standardization Program (NGSP).





Metabolic changes in DM

CHO:

1- ↓ glucose uptake in muscle & adipose tissues

2- ↑ glycogenolysis

3 ↑gluconeogenesis

Lipid:

1- ↑ lipolysis

2- ↑ fatty acid oxidation

3- ↑ production of ketone bodies (more in T1DM)

Protein:

1-↓ protein synthesis

2- ↑ protein degradation

Mechanisms of Increase Hepatic Glucose Output

↓ **Insulin** — inhibitory effect on glucagon secretion

⇩

↑**Glucagon**

⇩

↑Gluconeogenesis & glycogenolysis **(Liver)**

⇩

↑Plasma glucose

Mechanisms of Decrease of Peripheral Glucose Uptake

1/ muscle

↓ **Insulin**

⇩

↓Glucose & amino acid uptake

↑Protein breakdown

⇩

↑Plasma glucose ↑Plasma amino acids

2/Adipose Tissue

↓ **Insulin**

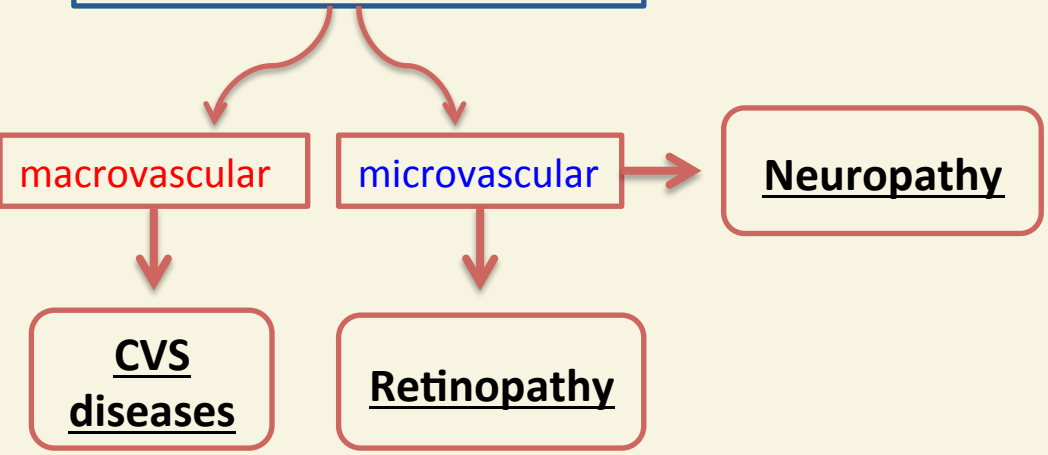
⇩

↓ Glucose uptake

⇩

↑Plasma glucose

Complication of DM



Advanced Glycosylation End Products (AGEs)

Chronic hyperglycemia → non-enzymatic combination between excess glucose & amino acids in proteins → formation of AGEs

AGEs may cross link with collagen → microvascular complications

The interaction between AGEs and their receptor (RAGE) may generate reactive oxygen species (ROS) → inflammation

Microvascular Complications

- Chronic hyperglycemia →

1- ↑ Advanced Glycation End products (AGEs) of essential cellular proteins → cellular defects

2- ↑Intracellular sorbitol → ↑ cell osmolality → cellular swelling

3- ↑ Reactive Oxygen Species (ROS) → oxidative stress → cell damage

Polyol pathway

Glucose is metabolized to sorbitol within the cells by aldose reductase

The role of sorbitol in the pathogenesis of diabetic complications is uncertain.

Hypotheses are:

1- During sorbitol production, consumption of NADPH → oxidative stress.

2- Sorbitol accumulation →

A- Increase the intracellular osmotic pressure → osmotic drag of fluid from extracellular space → cell swelling

B- Alteration in the activity of PKC → altered VEGF[1] activity→ altered vascular permeability

1-Vascular endothelial growth factor

Diabetic Retinopathy

A progressive microvascular complication of DM, affecting the retina of the eye

It cause blindness

Its prevalence ↑ with increasing duration of disease in both type 1 & 2 DM

After 20 years of the disease:

Is present in almost all T1DM

Is present in 50 – 80% of T2DM

Diabetic Nephropathy

- Occurs in both type 1 & type 2 DM
- The earliest clinical finding of diabetic nephropathy is microalbuminuria:
  - (the persistent excretion of small amounts of albumin (30-300 mg per day) into the urine)
- Microalbuminuria is an important predictor of progression to proteinuria:
  - (the persistent excretion of >300 mg albumin per day into the urine)
- Once proteinuria appears, there is a steady ↓ in the glomerular filtration rate (GFR)
- Finally, end-stage renal disease occurs

Diabetic Neuropathy

- Loss of both myelinated and unmyelinated nerve fibers

- Occurs in both type 1 & type 2 DM

- It correlates with the duration of DM & with glycemic control

Summary

- T1DM results from destruction of beta cells of the pancreas while T2DM is due to the development of insulin resistance.
- Genetics, Obesity , sedentary lifestyle and aging are the factors which may contribute in the development of insulin resistance.
- Criteria for diagnosis of DM includes assessment of **FPG** - **OGTT** - **A1C** .
- **Complications of DM are classified into :**
  - Macrovascular (CVS diseases)
  - microvascular (Neuropathy , Retinopathy)
- General Mechanisms for Diabetic Microvascular Complications:

✓ ↑ Advanced Glycation End products (AGEs) of essential cellular proteins → cellular defects

✓ ↑Intracellular sorbitol → ↑ cell osmolality → cellular swelling

✓ ↑ Reactive Oxygen Species (ROS) → oxidative stress → cell damage

- The earliest clinical finding of diabetic nephropathy is microalbuminuria then progression to proteinuria and decrease GFR and may end with end-stage renal disease .

TEST YOURSELF!

1. Regarding diabetic retinopathy, which one is incorrect:

A. Higher risk in type 1.

B. Microvascualr disease contributes in the progression of diabetic retinopathy.

C. Never happens in type 2.

D. Common complication.

2. Microalbiminuria is a complication occurs in:

A. Diabetic retinopathy.

B. Diabetic nephropathy.

C. Diabetic neuropathy.

D. Diabetic ketoacidosis.

3 . Which one of the following cut-off points of Hemoglobin A1C is used to diagnose diabetes?

A. Less than 6.5 %.

B. More than 6.5 %.

C. More than 5.6 % .

D. Less than 5.6 % .

4. All of the following are major metabolic changes seen in diabetes mellitus except:

A. Glycogenolysis.

B. Increased protein synthesis.

C. Increase lipolysis.

D. Increase production of ketone bodies.

5. Chronic hyperglycemia will lead to non-enzymatic combination between excess glucose and amino acids in proteins which is known as:

A. Polyol pathway.

B. ROS.

C. Advanced Glycosylation End Products.

D. None of the above.

6. Microvascualr complication seen in DM, may result form cross linkage between:

A. AGEs and Amyloid.

B. Cytokines and IL-1.

C. AGEs and Interferon Alfa.

D. AGEs and Collagen.

1-C 2-B 3-B 4-B 5-C 6-D

TEST YOURSELF!

7.Sorbitol accumulation in retina, nerves, and kidney is responsible for the diabetic complication, because these tissues do not have the following enzyme:

A. Sorbitol hydroxylase.

B. Aldos Reductase.

C. Sorbitol dehydrogenase.

D. DGlucokinase.

8. The earliest clinical finding of diabetic nephropathy is:

A. Microalbuminuria.

B. Macroalbuminuria.

C. Proteinuria.

D. Albumin excretion is normal.

9.Testing the levels of which one of the following estimates glycemic control in the last 1-2 months:

A. FBG.

B. HBA1C.

C. FFA.

D. Insulin.

10. Which one of the following is a metabolic effect of insulin:

A. ↑ Lipolysis.

B. ↑protien synthesis.

C. ↑ Glycogenolysis.

D. ↓ Lipolysis.

Answers :

7-C 8-A 9-B 10-D

THANK YOU ...

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