Metabolic Changes in Diabetes Mellitus

Biochemistry Teamwork

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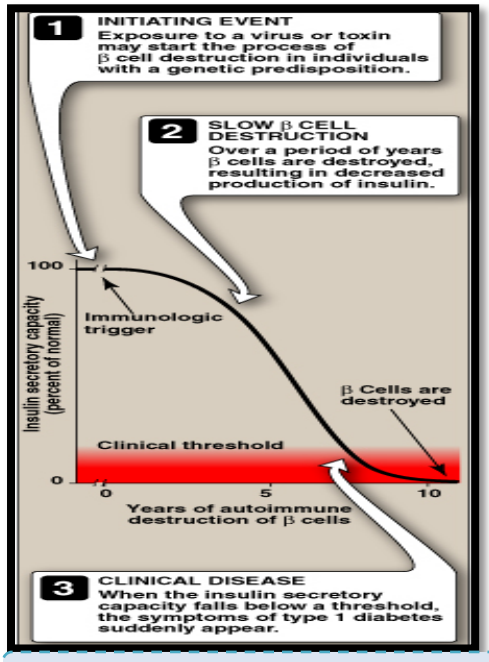
Metabolic Changes in Diabetes Mellitus

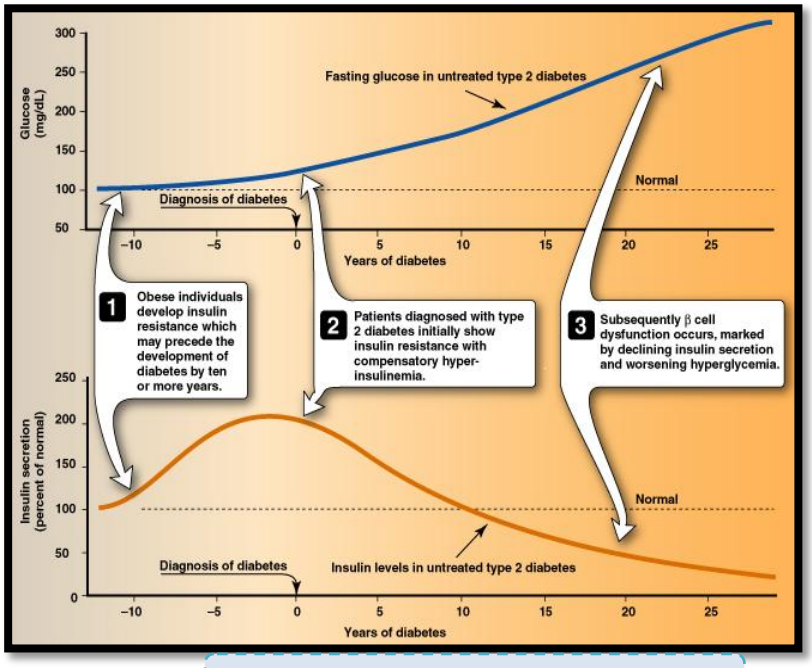
- **Background**
- Differences between type 1 and type 2 DM
- Natural course of T1DM
- Natural course of T2DM
  - **Diagnostic criteria for DM**
  - **Metabolic changes in DM**
- Increase of hepatic glucose output
- Decrease of glucose uptake
- Inter-organ relationship in T1DM and T2DM
  - **Mechanisms of diabetic complications**

Comparison of type 1 and type 2 DM

	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	10 Million = 90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar coma
TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin



Natural course of T1DM



Progression of T2DM

- In the beginning of type two there will be hyperinsulinemia as a compensatory mechanism but after a while and in the end stage will have decreased insulin level .
- The onset of action in type one is abrupt and is gradual in type two .
- In gestational diabetes we give insulin because it is safe to the baby and this is caused because of increased level of some anti-insulin hormones such as estrogen .

Criteria for diagnosis of DM: " Dr.Reem said: the most important nom. here is >6.5 % "

Categories of increased risk for diabetes*
FPG 100-125 mg/dL (5.6-6.9 mmol/L) [IFG]
2-h PG on the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L) [IGT]
A1C 5.7-6.4 percent

FPG: fasting plasma glucose; IFG: impaired fasting glucose; PG: post glucose; OGTT: oral glucose tolerance test; IGT: impaired glucose tolerance; A1C: glycated hemoglobin.

The period between 5.6 to 6.9 , 7.8 to 11 and 5.7 to 6.4 is called "prediabetic period"

Criteria for the diagnosis of diabetes
1. A1C ≥6.5 percent. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
2. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

A1C: glycated hemoglobin; NGSP: National glycohemoglobin standardization program; DCCT: Diabetes control and complications trial; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.
* In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

-When we have a cardinal symptom of DM , as well as one of the tests is positive this is enough for diagnosis but if there is no symptoms we have to confirm the test again .
-When fasting glucose blood level = 100-125 mg/dl It is referred as impaired fasting glucose tolerance , the patient need to modify his/her life style and have exercise to prevent or at least delay

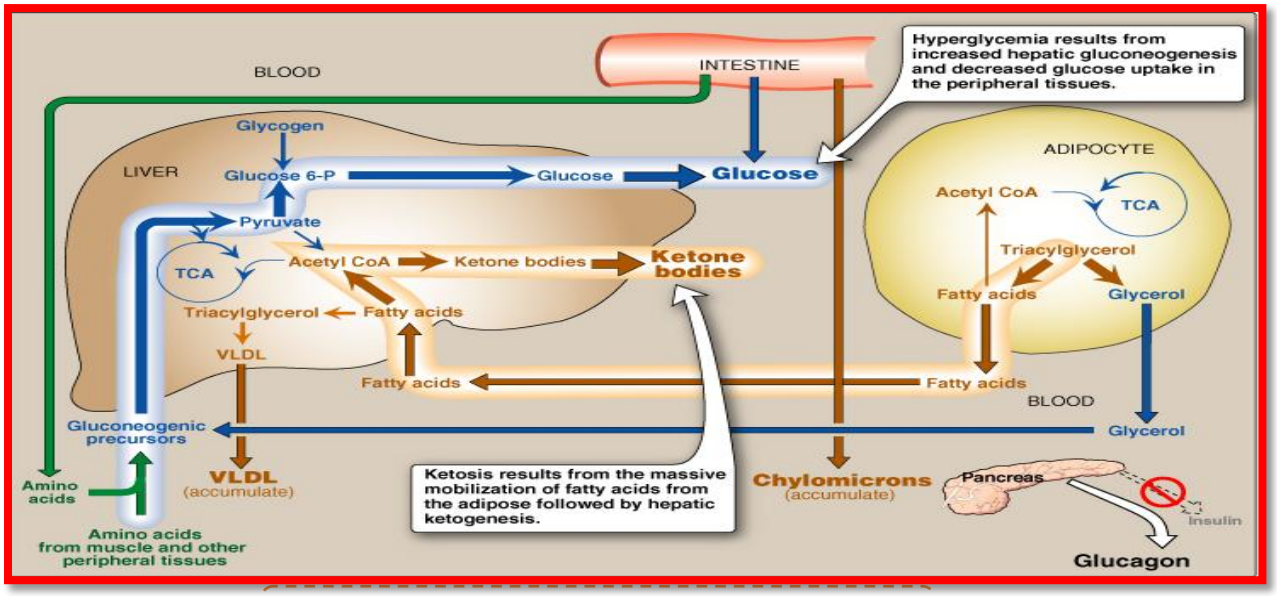
HEMOGLOBIN A1C

- **Hemoglobin A1C (A1C) is the result of non enzymatic covalent glycosylation of hemoglobin.**
- **It is used to estimate glycemic control in the last 1-2 months**
- **Recently, A1C is recommended for the detection of T2DM**
- **A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.**
- **A1C cut-off point of >6.5 % is used to diagnose diabetes.**
- **A1C values also correlate with the prevalence of retinopathy**
- **Assays for A1C has to be standardized according to the National Glycohemoglobin Standardization Program (NGSP).**

Metabolic Effects of Diabetes Mellitus

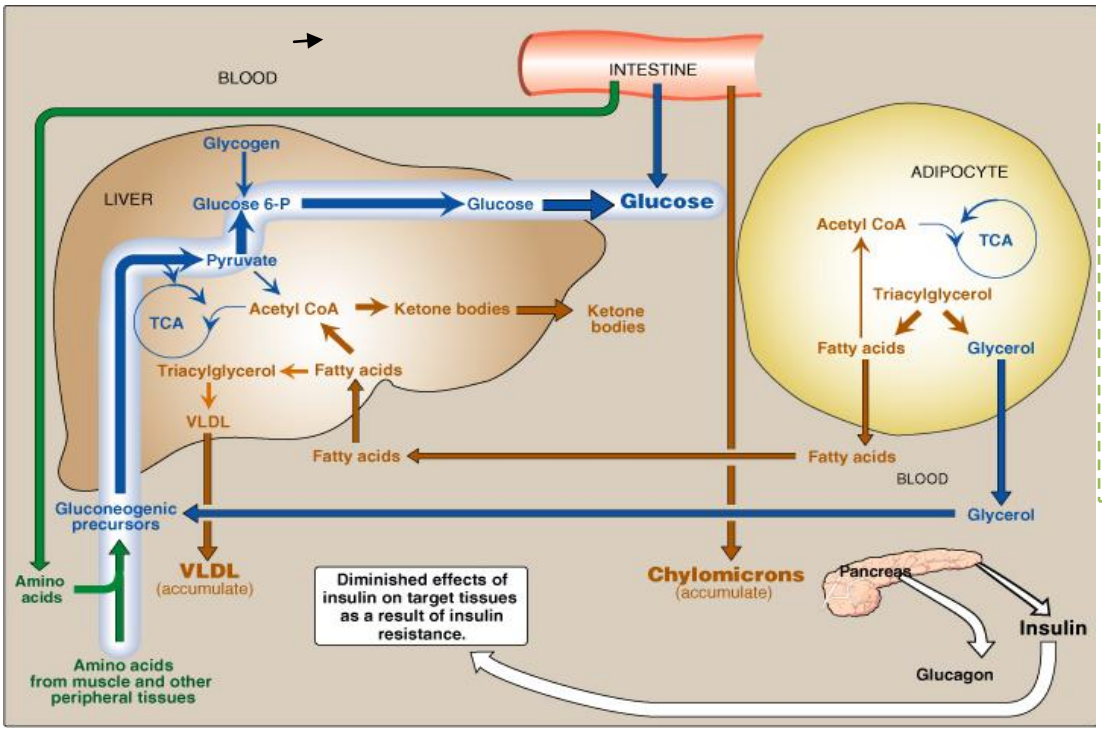
- **Absolute or relative insulin deficiency →**

1. ↓ **Glucose uptake (muscle & adipose tissue)**
2. ↑ **Glucose production (liver)**



Imp

Intertissue Relationship in T1DM



- In type one there is absolute insulin deficiency while in two relative insulin deficiency.. so there will be more lipolysis
  ↑ ketogenesis (fatty acid toxicity)

Intertissue Relationship in T2DM

Major Metabolic changes in DM

Absolute or relative insulin deficiency

↓

Multiple metabolic effects

↓

CHO metabolism

↓ Glucose uptake by certain tissues (adipose tissue & muscle)

↑ Glycogenolysis

↑ Gluconeogenesis

Lipid metabolism

↑ Lipolysis

↑ Fatty acid oxidation

↑ Production of Ketone bodies

Protein metabolism

↓ Protein synthesis

↑ Protein degradation

Mechanisms of Increase Hepatic Glucose Output

↓ Insulin

↓ Inhibitory effect on glucagon secretion

↑Glucagon

↑Gluconeogenesis & glycogenolysis (Liver)

↑Plasma glucose

Mechanisms of Increase Hepatic Glucose Output

Muscle

↓ Insulin

↓Glucose & amino acid uptake

↑Protein breakdown

↑Plasma glucose

↑Plasma amino acids

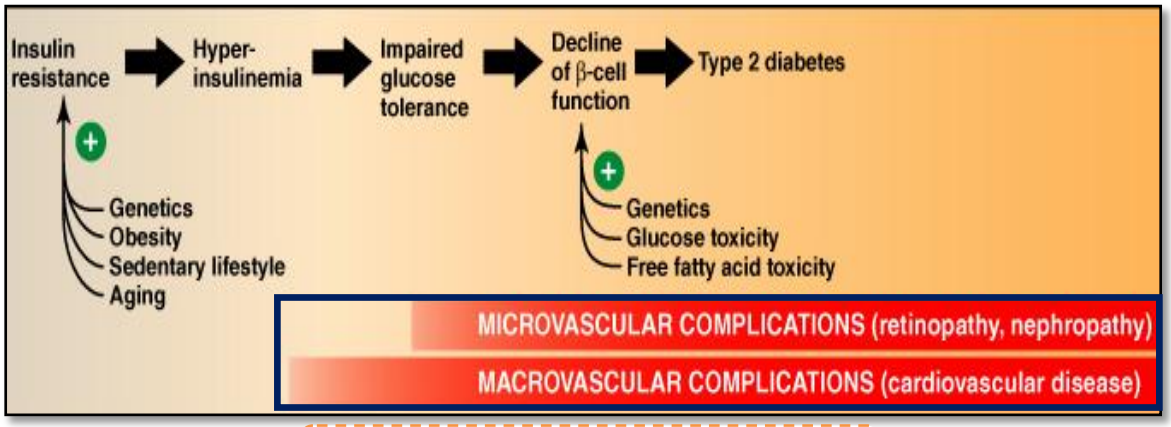
Adipose Tissue

↓ Insulin

↓ Glucose uptake

↑Plasma glucose

Mechanisms of Diabetic Complications



Typical progression of T2DM

General Mechanisms for Diabetic Microvascular Complications

Chronic hyperglycemia →

1. ↑ **AGEs of essential cellular proteins → cellular defects**
2. ↑**Intracellular sorbitol → ↑ cell osmolality → cellular swelling**
3. ↑ **ROS → oxidative stress → cell damage**

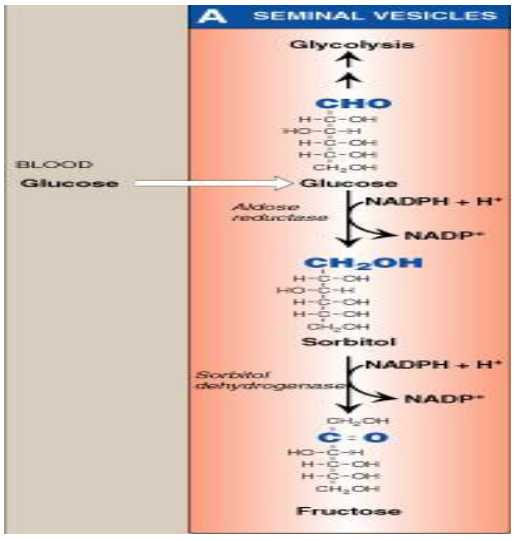
Advanced Glycosylation End Products (AGEs)

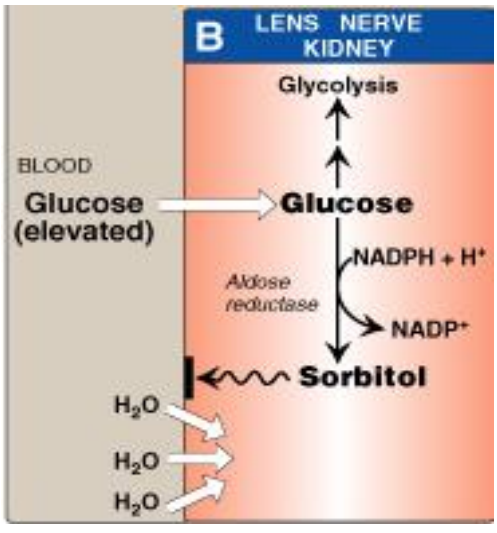
- **Chronic hyperglycemia →non-enzymatic combination between excess glucose & amino acids in proteins → formation of AGEs**
- **AGEs may cross link with collagen → microvascular complications**
- **The interaction between AGEs and their receptor (RAGE) may generate reactive oxygen species (ROS) → inflammation**

Polyol pathway(Sorbitol Metabolism , A Mechanism for Diabetic Complications)

- **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:**
  - **During sorbitol production, consumption of NADPH → oxidative stress.**
  - **Sorbitol accumulation →**
    - **Increase the intracellular osmotic pressure → osmotic drag of fluid from extracellular space → cell swelling**
    - **Alteration in the activity of PKC → altered VEGF activity→ altered vascular permeability**

Normal





Abnormal

Retina ,kidney ,neurons are deficient in sorbitol dehydrogenase which converts Sorbitol into fructose and this will lead to diabetic complications

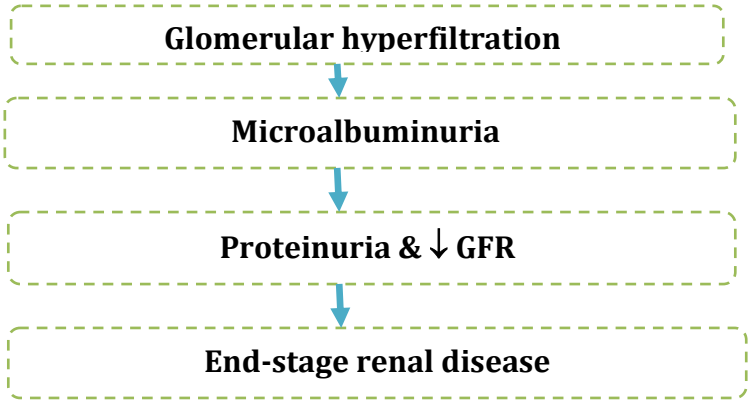
Diabetic Retinopathy

- A progressive microvascular complication of DM, affecting the retina of the eye
- A major cause of morbidity in DM (→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.(is detected by nephelometer)
- (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

Sequence of Events in Diabetic Nephropathy



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

Insulin Resistance

Can be cause by insulin abnormality, insulin receptor abnormality , or abnormality in post-receptor events(commonest)

Review Question

1. **Regarding diabetic retinopathy, which is incorrect:**
   A. Higher risk in type 1
   B. Microvascualr disease contributes to 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. CIncrease 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 know 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

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. Proteinuria
   B. Macroalbuminuria
   C. Microalbuminuria
   D. Albumin excretion is normal

1-C 2-B 3-B 4-B 5-C 6-D 7-C 8-C