Biochemistry of the Endocrine Block

Metabolic Changes in Diabetes Mellitus

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Lecture outline:

- **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 : (diabetes is a metabolic disease)

(This schedule differentiate between type 1&2 classically, means now there are some interferes between the 2 types)

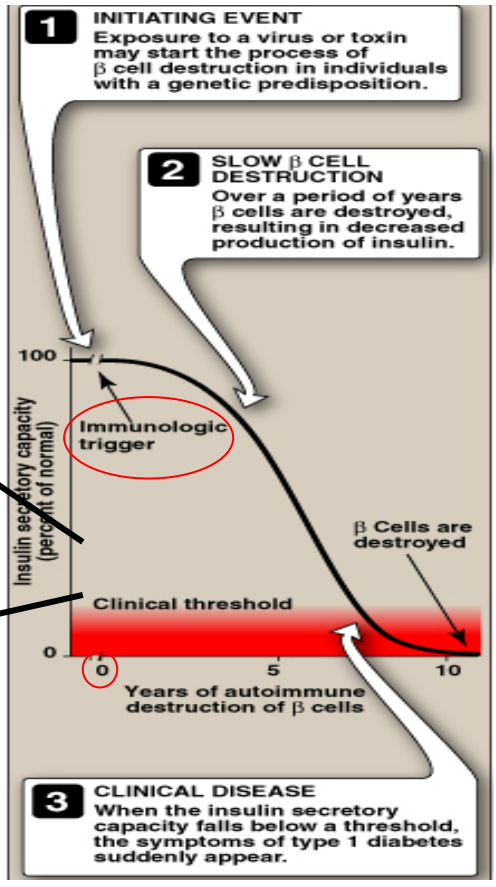
	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	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

-/+ insulin = in the late stage of the disease pt may take insulin or in case of hyperosmolarity.

Natural course of T1DM : (live on insulin)

When in it crosses the red line the symptoms will appear (approximately less than 10% of the pancreas is working)

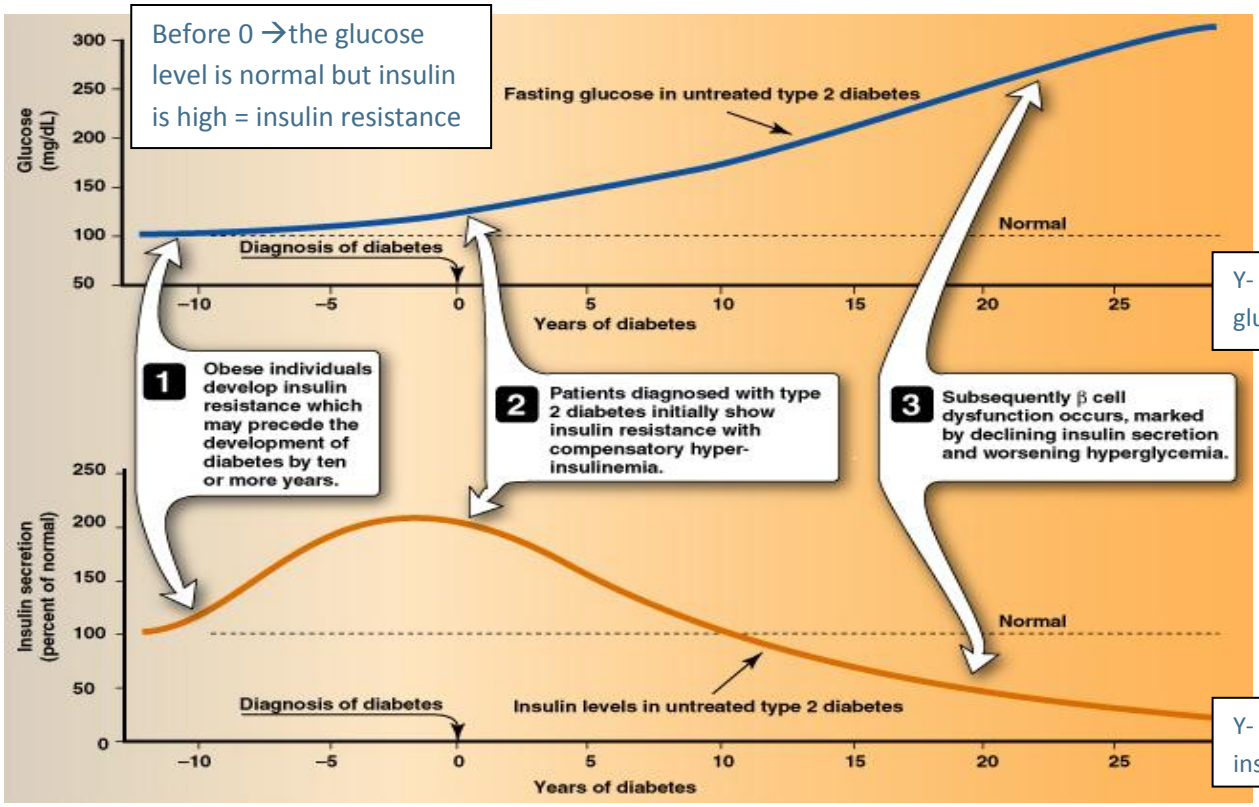
Triggers (e.g: toxins or viruses -until now unknown)→ stimulate Ab→ attack pancreas (destruction)→ after years → DM



Progression of T2DM :

Sequence: obesity→ peripheral insulin resistance →hyper-insulinemia (at the beginning of the disease)→β cells dysfunction + hyper-glycemia→ hyper-osmolarity (due to increase glucose level)→coma (non ketotic).

Curve:
(-)= pathology of the disease is going on[No symptoms][The resistance period]
(0)=diagnostic point [symptoms appearance].



Criteria for Diagnosis of DM* : (*American Diabetes Association (ADA), 2011)

Red box → You have to memorize it.

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

NORMAL 5.5 < IFG 5.6-6.9 < 7 DIABETIC

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

Pre-diabetic (=increased risk for diabetes) is either: 1- IFG[when we take a sample from the pt blood after 12 hours of fasting → glucose is high but not enough to diagnose the pt as diabetic]
2- IGT[when we take a sample from the pt blood after 2 hours of a meal→ glucose is high but not enough to diagnose the pt as diabetic]

4 criteria (we use one of the methods to diagnose diabetes)

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.

HEMOGLOBIN A1C: (Hb A1c= Glycated Hb(glucose on Hb)

- 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 "due to the 120 days life span of RBCs"
- 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. (If a 100 Hb contain 6.4 HbA1c → the result is normal)
- A1C values also correlate with the prevalence of retinopathy
- Assays for A1C has to be standardized according to the National Glycohemoglobin Standardization Program (NGSP).

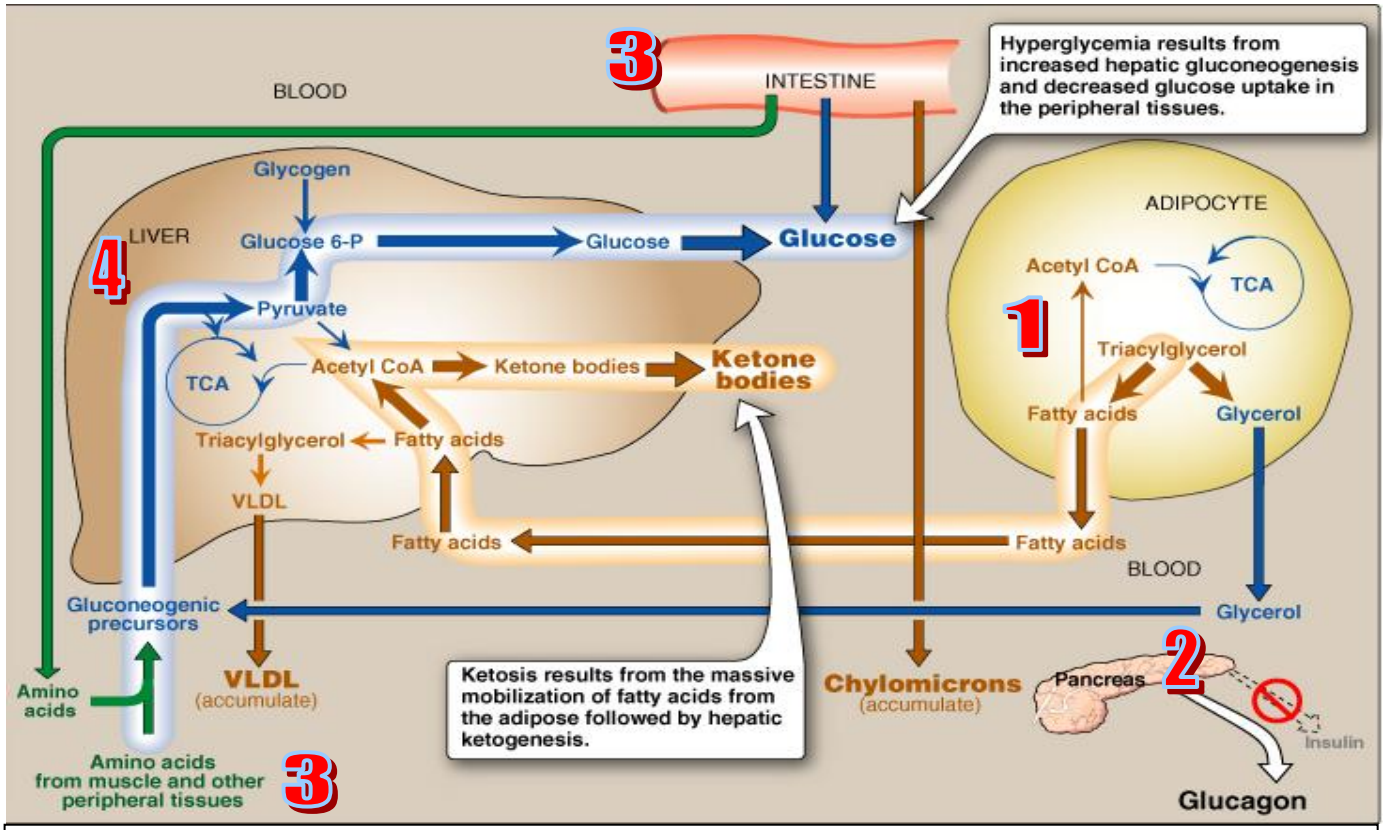
Metabolic Effects of Diabetes Mellitus :

- Absolute or relative insulin deficiency →
  1. ↓ Glucose uptake (by muscle & adipose tissue)
  2. ↑ Glucose production (from liver)

↑ glucose level due to these 2 reasons

Intertissue Relationship in *T1DM* :

IMPORTANT



- Gluconeogenesis(synthesis of glucose from non CHO resources) + Lipolysis + Glucose uptake by the tissues→ controlled by insulin.
- In diabetes there will be muscle wasting.
- In T1DM the upper hand is for glucagon. (glucagon stimulates gluconeogenesis)
- Gluconeogenesis is stimulates by 4 things → aa from the muscle + glycerol from adipose tissue + glucagon from pancreas + absence of insulin.

1- In adipose tissue: TAG broken down into→ FFA(↑↑also cause insulin resistance) .
→ Glycerol → gluconeogenesis (in the liver) .

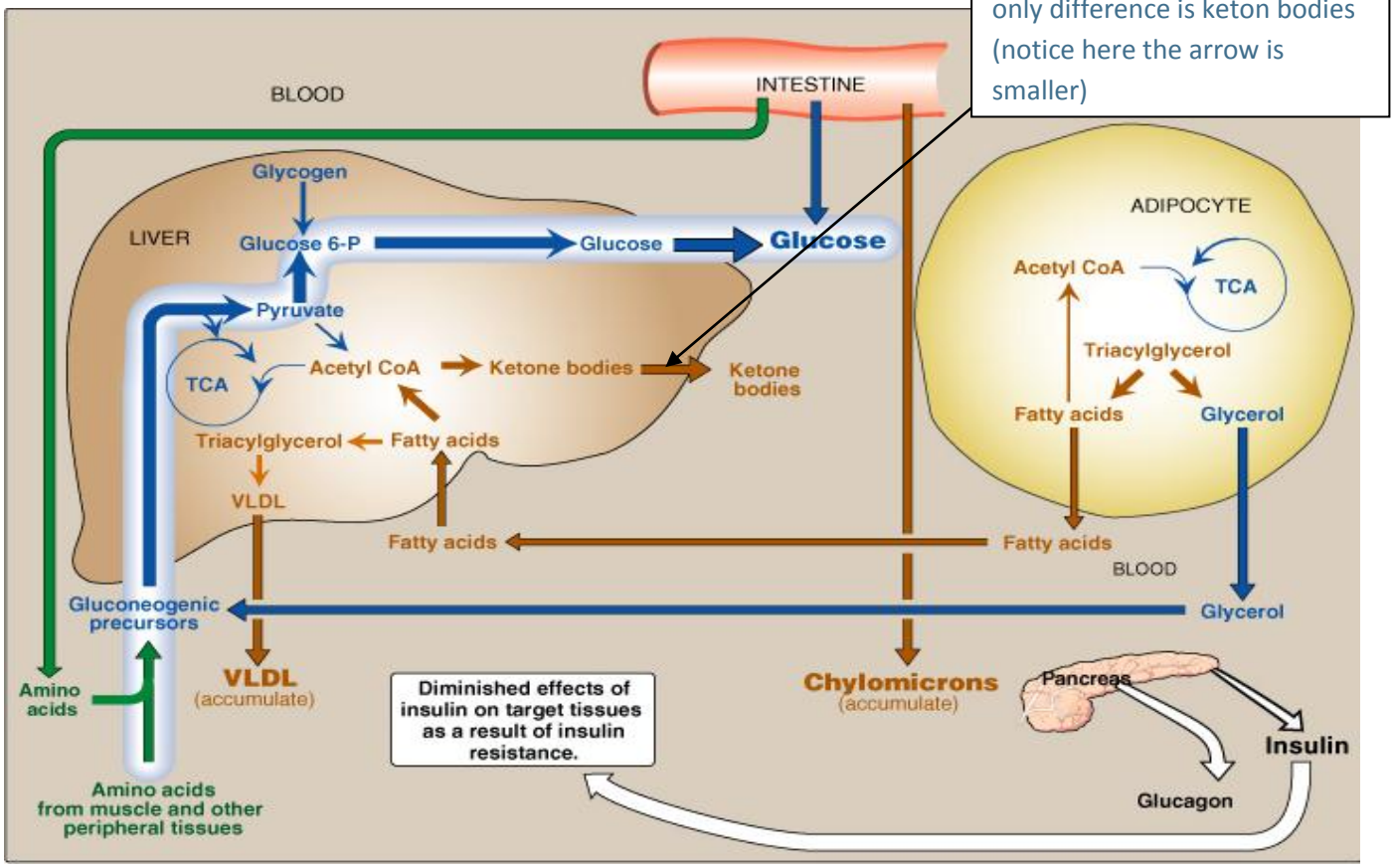
2- ↑ production of glucagon from pancreas.

3- ↑ catabolism of protein in the muscles and intestine (=↑aa)

4- In the liver : → Gluconeogenesis
→ FFAs → Oxidized into Acetyl CoA
→ Combined with TAG→VLDL
→ Synthesis of keton bodies , (keton bodies are acids) [keton bodies are inhibited by insulin that's why there is no keton bodies in T2DM]

Intertissue Relationship in *T2DM* :

Same as the previous one the only difference is keton bodies (notice here the arrow is smaller)



Major Metabolic changes in DM :

Absolute or relative insulin

⇩

Multiple metabolic effects (imp)

CHO metabolism

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

↑ Glycogenolysis

↑ Gluconeogenesis

Lipid metabolism

↑ Lipolysis

↑ Fatty acid oxidation

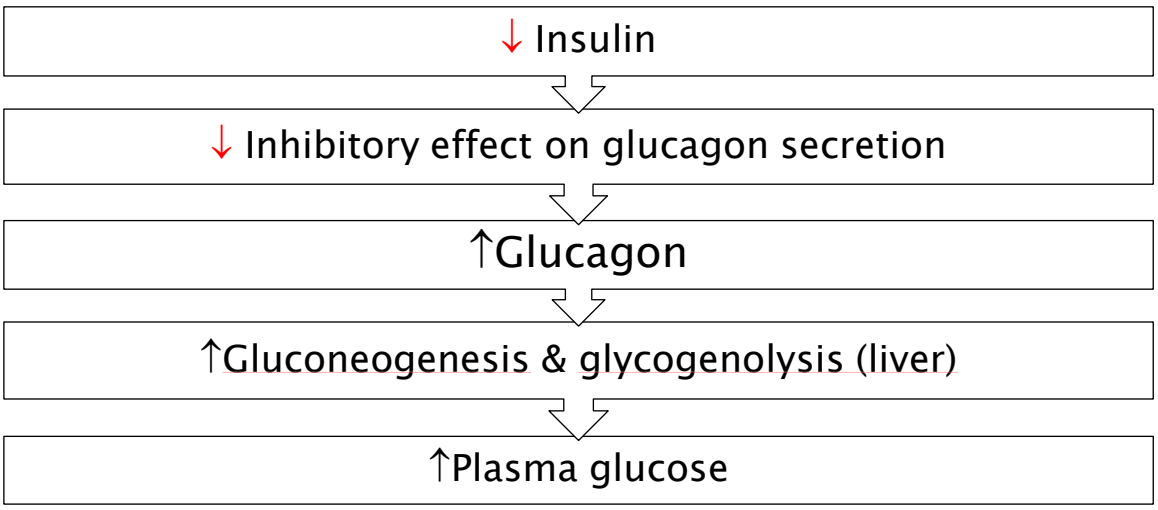
↑ Production of Ketone bodies (in liver)

Protein metabolism

↓ Protein synthesis

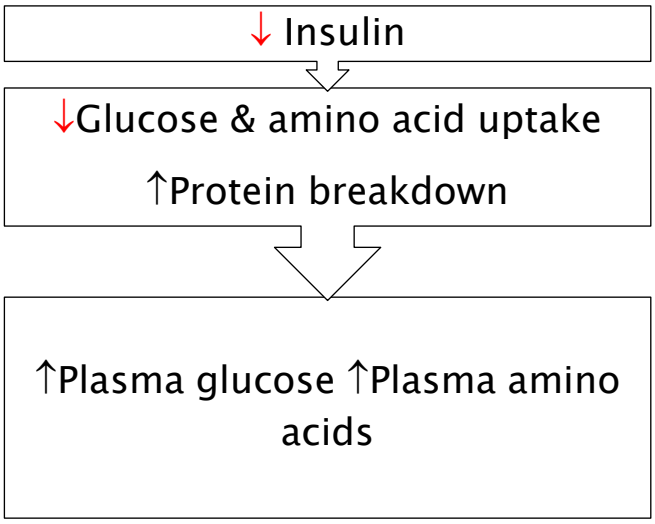
↑ Protein degradation

Mechanisms of Increase Hepatic Glucose Output:

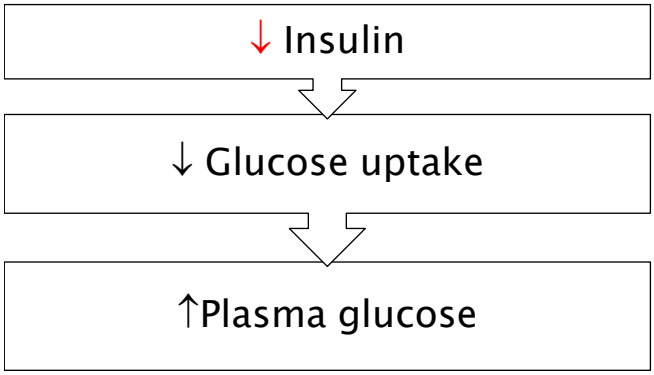


Mechanisms of Decrease of Peripheral Glucose Uptake :

Muscles

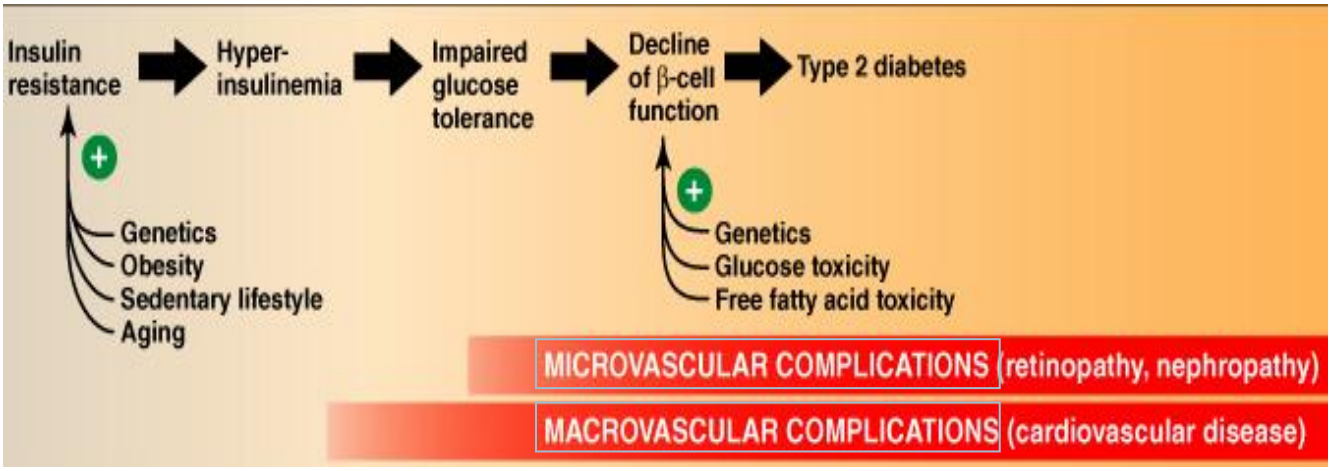


Adipose Tissue



Mechanisms of Diabetic Complications : → Micro
→Marco (CVS Diseases)

Typical Progression of T2DM :



General Mechanisms for Diabetic Microvascular Complications :

- Chronic hyperglycemia →
  - 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

Advanced Glycosylation End Products (AGEs) : (glucose can also bind to another proteins than Hb which in this case will called 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

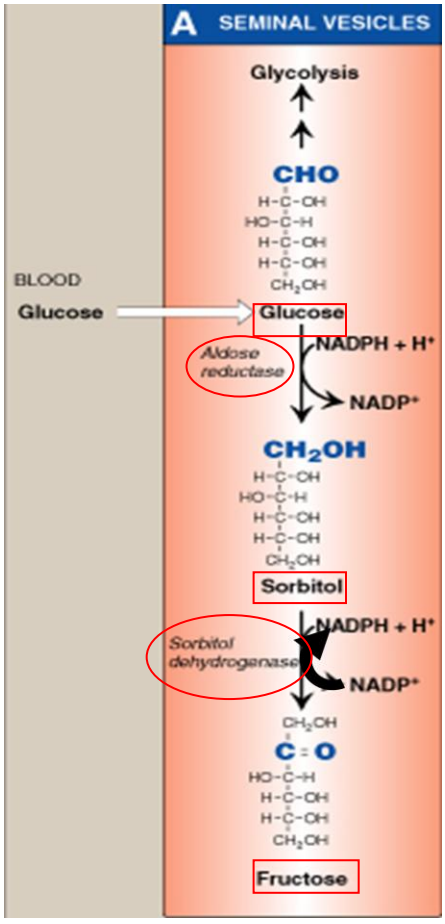
Polyol pathway :

- 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

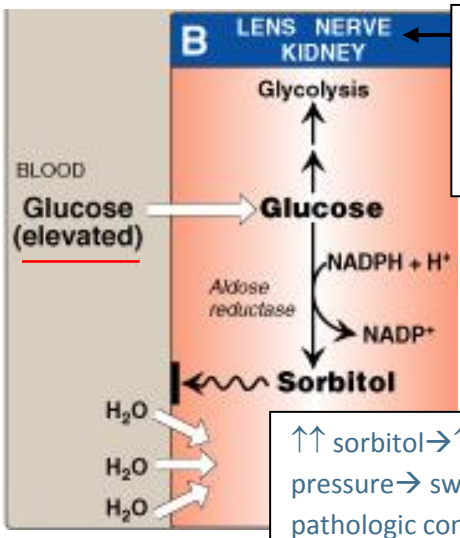
Sorbitol(sugar alcohol) **Metabolism = Polyol Pathway**
(A Mechanism for Diabetic Complications)

Normal cells can take glucose and convert it into fructose by 2 reactions [you should know these reactions] if these cells need it (e.g. : sperms)

Normal



Ubnormal



These cells don't have the 2nd enzyme.

↑↑ sorbitol→↑ osmotic pressure→ swelling→ pathologic condition

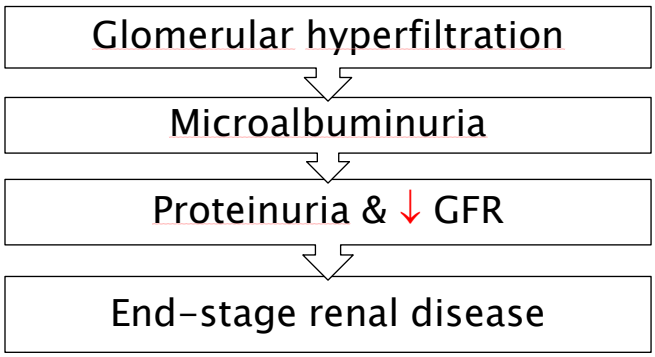
Diabetic Retinopathy :

- 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:
  - (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: (imp)
  - (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

Summary

- ✓ Type 1 → β cell destruction
- ✓ Type 2 → insulin resistance
- ✓ Pre-diabetics:
  - FPG (5.6 - 6.9 mmol/l)
  - 75 OGTT (7.8 – 11 mmol/l)
  - A1C (5.7 – 6.4 %)
- ✓ Diabetics:
  - A1C > 6.5%
  - FPG > 7mm/l
  - OGTT > 11.1 mmol/l
- ✓ Classic symptoms of hyperglycemia or hypergylcemic crisis + random plasma glucose > 11.1 mmol/l
- ✓ 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 "due to the 120 days life span of RBCs"
- ✓ Recently, A1C is recommended for the detection of T2DM
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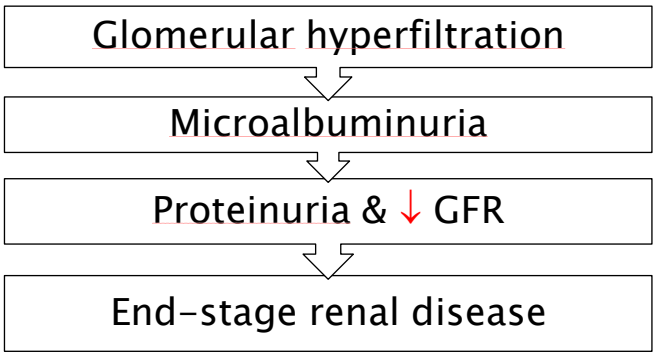
- ✓ **Diabetic Nephropathy:**



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