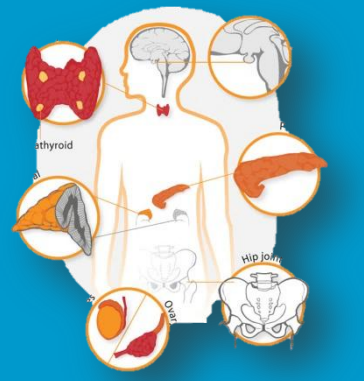
[lecture 7]

Metabolic Changes in Diabetes Mellitus



Endocrine system

Biochemistry Team

Teams

The Objectives

- **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**

Red = Import-ant

Blue = explain

Green = addition notes

Done By : Yara AlSalloum & Ameera AlAmri

Reviewed By : Abdulaziz Alanazi

Mind Map

- Differences between T1 and T2 DM
- Natural course of T1DM & T2DM
- Diagnostic criteria for DM
- Metabolic changes in DM
- Mechanisms of diabetic complications

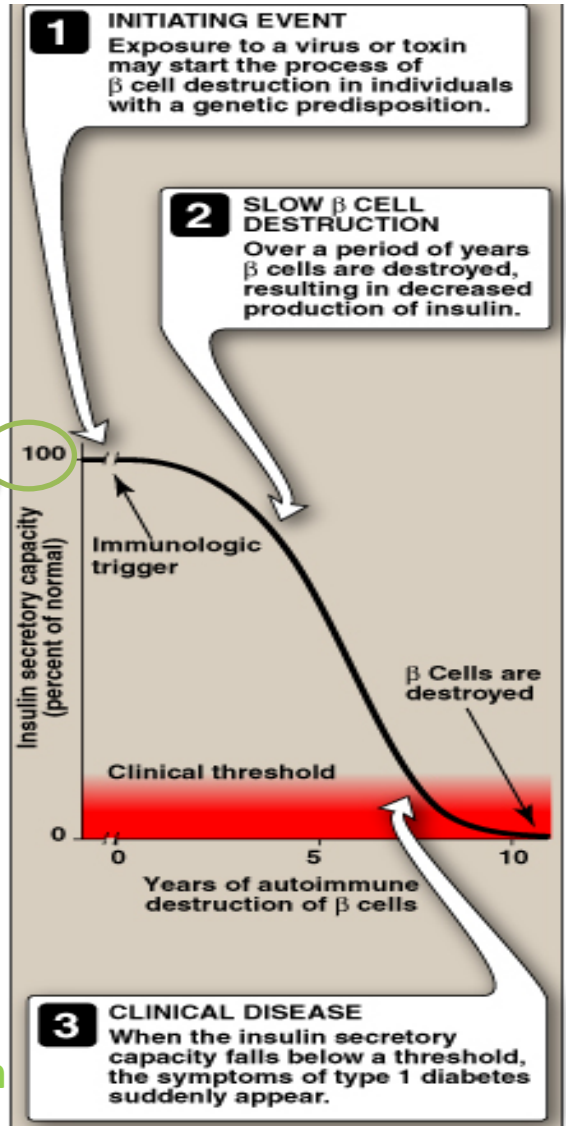
Comparison between Type 1 and Type 2 Diabetes

	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 Because there is no Insulin	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin

- Type 1 is autoimmune and is usually associated with other immune disorders such as SLE
- Type 2 Diabetes may affect children
- Type 2: There is peripheral resistance (muscle & adipose tissue) so the pancreas will try to compensate for insulin (insulin resistance & hyperinsulinism) but in the late stages the beta cells will get exhausted and insulin levels will fall (patients need administration of insulin)
- Type 1 Diabetes: Diabetic ketoacidocis (DKA) coma
- Type 2 Diabetes: Hyperosmolar/hyperglycemic (non ketotic) coma

DM T2

Natural Course of T1DM

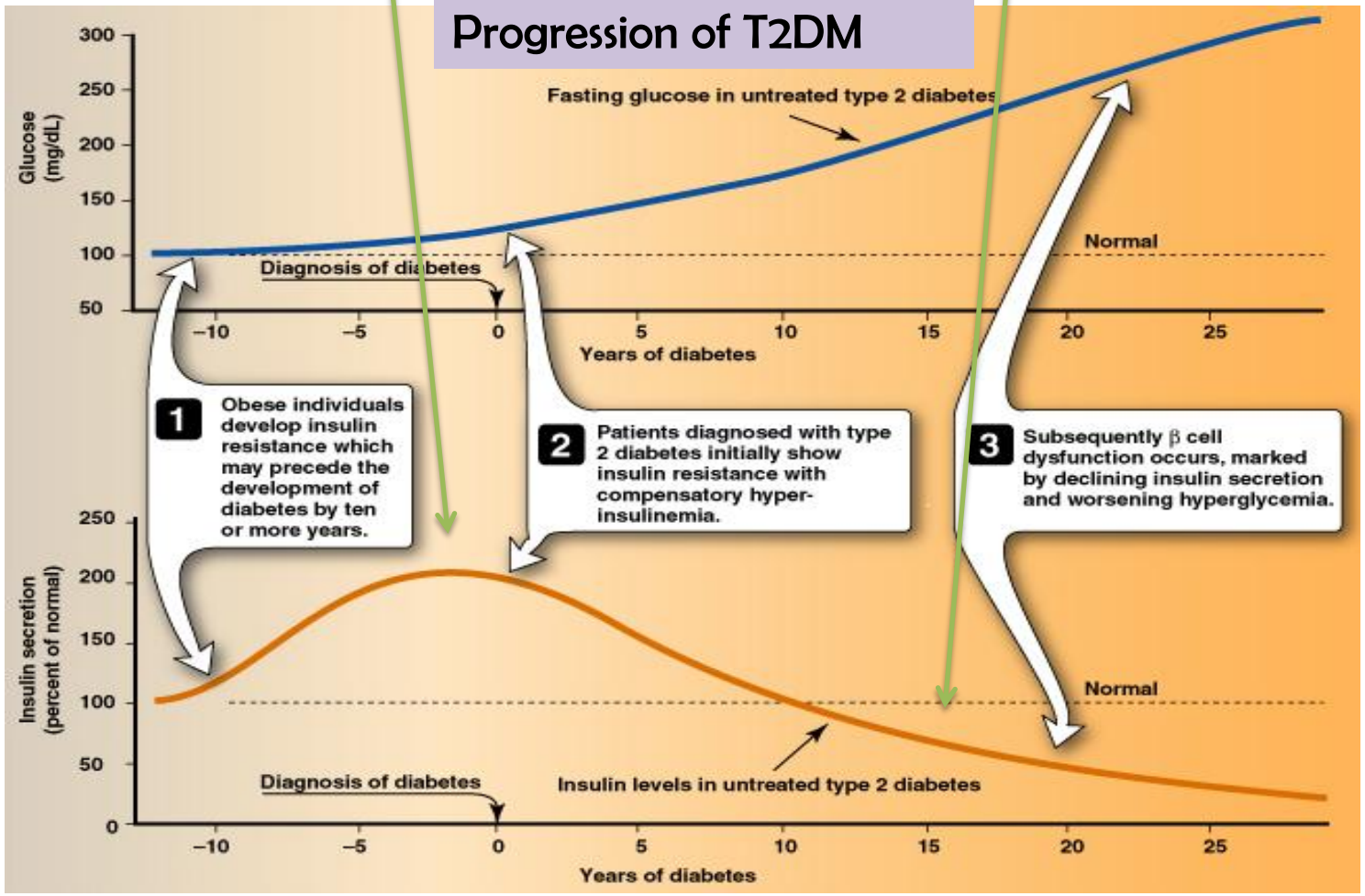


Pancreas's highest capacity to secrete insulin

Increase in the curve because of pancreatic over compensation

when it falls = exhaustion of beta cells

Progression of T2DM



Criteria for Diagnosis of DM (Prediabetes)

By the American Diabetes Association (ADA), 2014

Categories of increased risk for diabetes*

FPG 100-125 mg/dL (5.6-6.9 mmol/L) [IFG]
OR
2-h PG on the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L) [IGT]
OR
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.

Dr. Reem said (mmol/L) is the unit used in Saudi Arabia

Criteria for Diagnosis of DM (DM)

By the American Diabetes Association (ADA), 2014

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

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

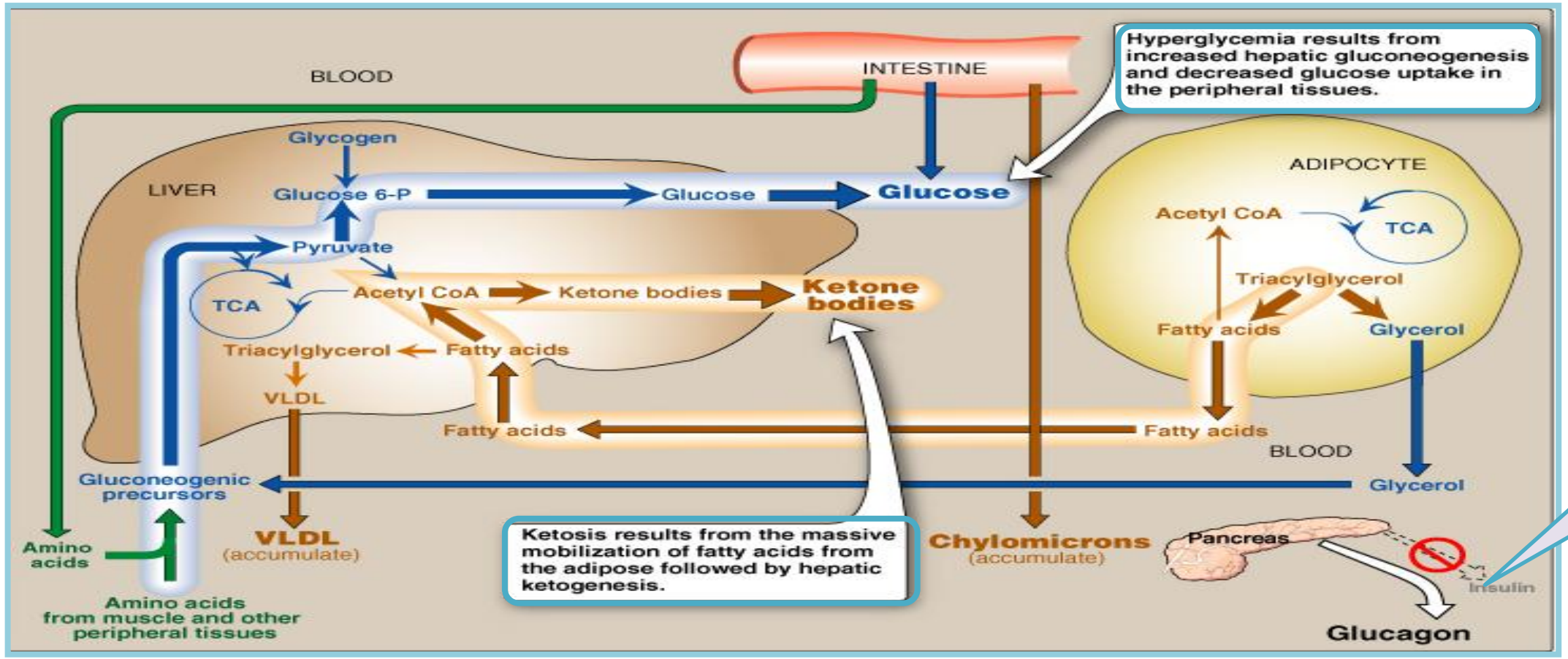
Absolute or relative insulin deficiency:

1. ↓ Glucose uptake (by muscle & adipose tissue)

2. ↑ Glucose production (from liver)

Relative Insulin Deficiency: The patient has enough insulin but there is peripheral resistance

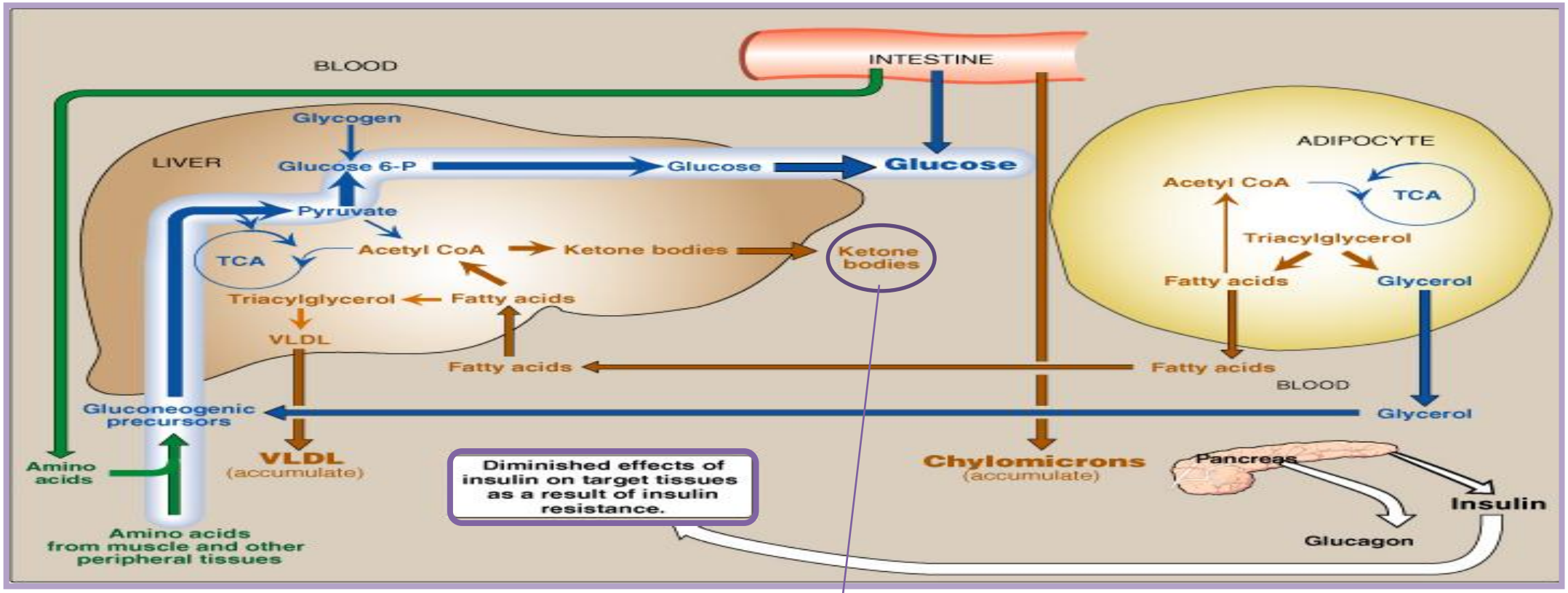
Intertissue Relationship in T1DM



There is no insulin in T1DM

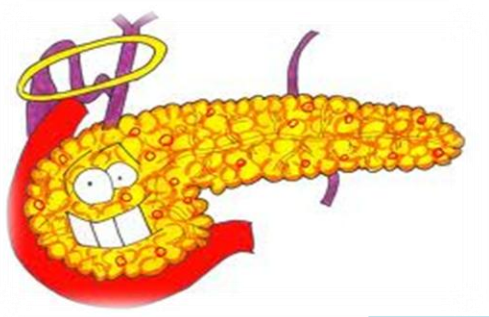
- Insulin inhibit synthesis <u>of ketone bodeies</u> ,so no insulin lead to synthesis of ketone bodies **and increase in lipolysis**
- Diabetic patient has **dyslipidemia** because of increase VLDL and chylomicrons
- In addition absence of insulin lead to **protien catabolism** >>> increase amino acid production
- All of these **increase gluconeogenesis** lead to increase blood glucose level

Intertissue Relationship in T2DM



- Small amount of insulin can **inhibit ketoneogenesis** that's why not common to see ketoacidosis in T2DM
- Free fatty acid production will be less than T1DM

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 (in liver)

Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

**DM is not a disease of carbohydrate metabolism only

Glucose

Mechanisms of Increase Hepatic Glucose Output

↓ Insulin

↓ Inhibitory effect on glucagon secretion

↑Glucagon

↑Gluconeogenesis & glycogenolysis

↑Plasma glucose

Mechanisms of Decrease of Peripheral Glucose Uptake

Muscle

↓Insulin

↓Glucose & amino acid uptake

↑Protein breakdown

↑Plasma glucose ↑Plasma amino acids

Adipose Tissue

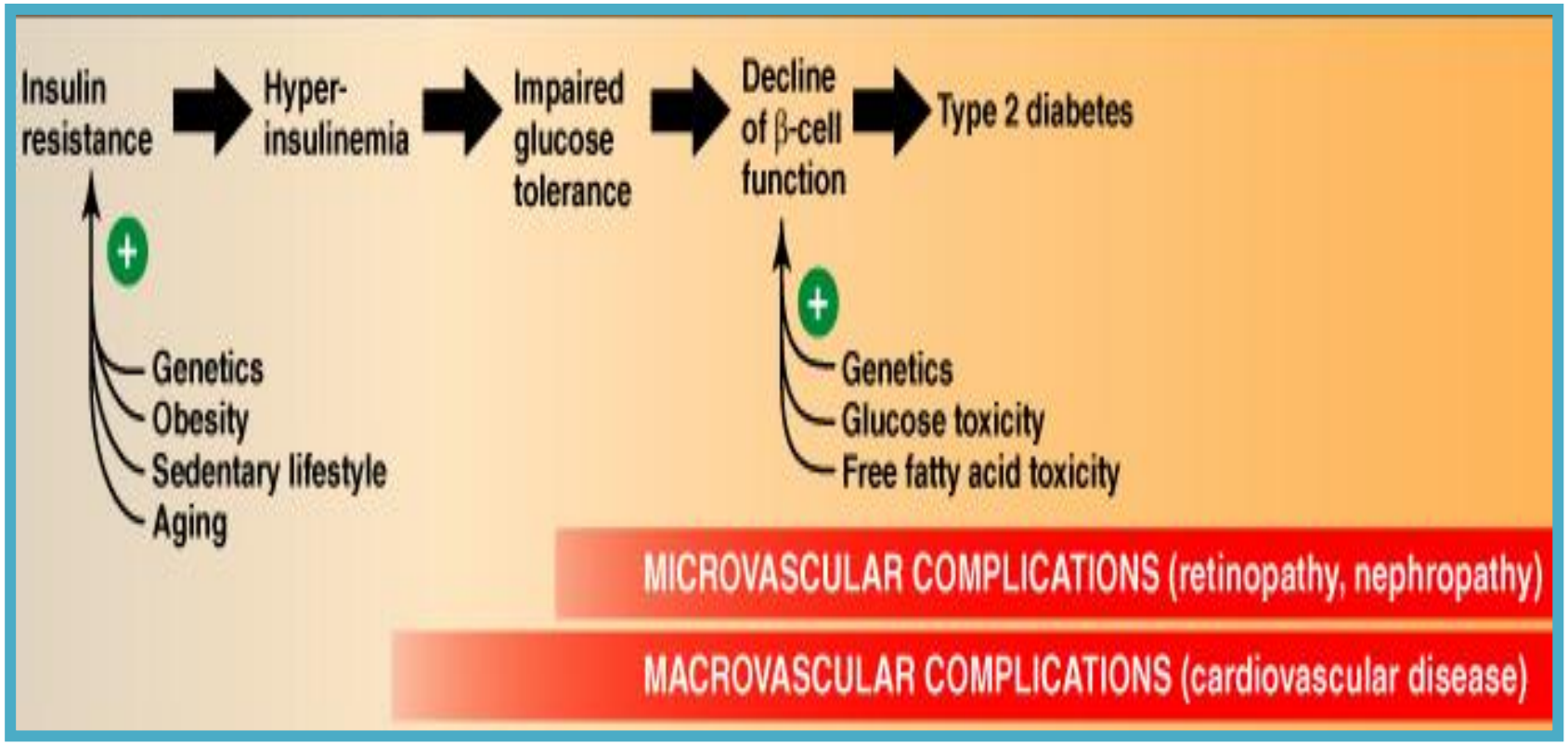
↓Insulin

↓Glucose uptake

↑Plasma glucose

*GLUT4 receptor only in muscle and adipose tissue and these receptors sensitive to insulin. When there is absence of insulin it can not uptake the glucose

Typical Progression of T2DM



Vessels with small diameter → microvascular complication

Vessels with big diameter → macrovascular complication

Mechanisms of Diabetic Complications

*General Mechanisms for Diabetic Microvascular Complications:

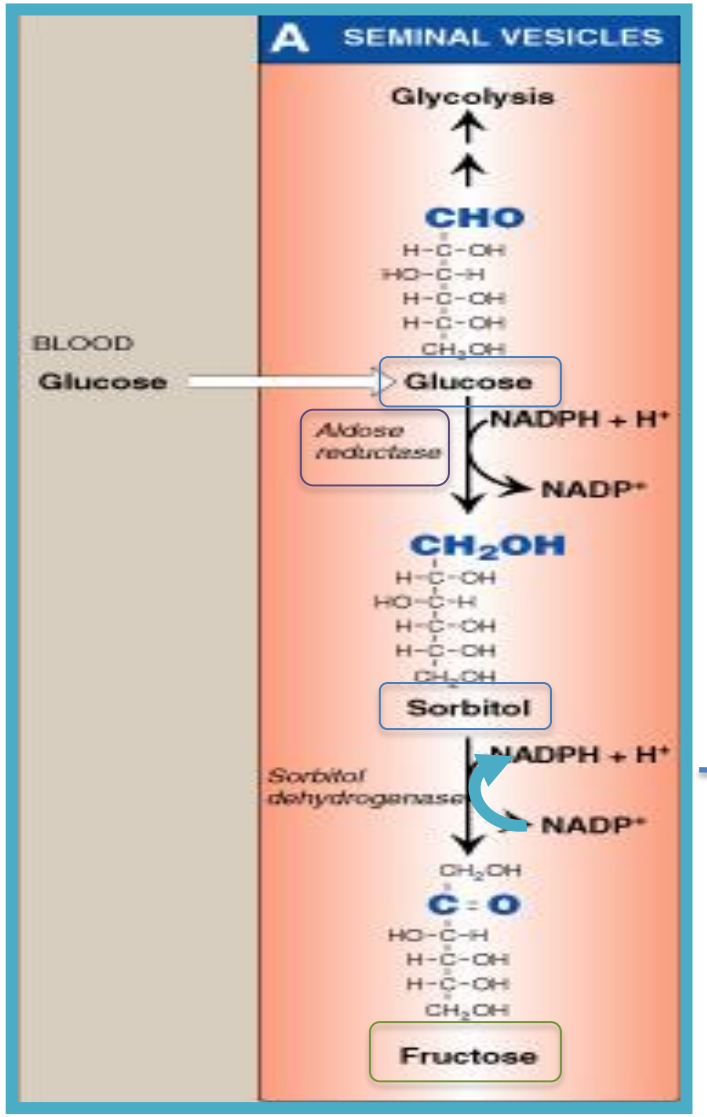
Chronic hyperglycemia

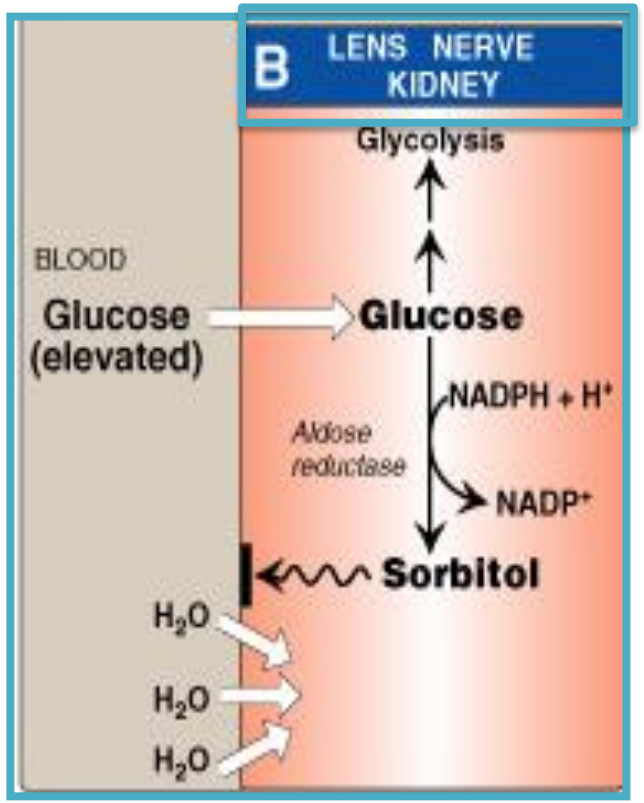
- ↑ Advanced Glycation End products (AGEs) of essential cellular proteins → cellular defects (glycation of these proteins affect functions)
- ↑Intracellular sorbitol → ↑ cell osmolality → cellular swelling
- ↑ Reactive Oxygen Species (ROS) → oxidative stress → cell damage

- 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

Sorbitol Metabolism
Polyol Pathway
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 (important for antioxidant)→ oxidative stress.
  - Sorbitol accumulation →
    1. **Increase the intracellular osmotic pressure** → osmotic drag of fluid from extracellular space → **cell swelling**
    2. Alteration in the activity of PKC → altered VEGF (permeability factor)activity→ altered vascular permeability





Normally sorbitol is converted to fructose by sorbitol dehydrogenase enzyme but this enzyme is not present in all the tissues such as the lens, Nerves and kidney.(Look above)

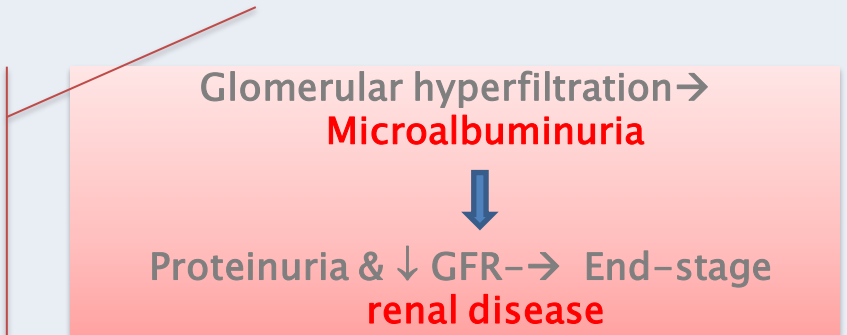
Complications

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:**
  - (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

- DM is a heterogeneous group of syndromes characterized by ↑ FBG (Fasting Blood Glucose)
- This↑ FBG is caused by a relative (in T2DM) or absolute (in T1DM) deficiency in insulin
- In T1DM there is autoimmune attack on β cells following a trigger from the environment and a genetic determinant.
- The metabolic abnormalities in T1DM:
  - include hyperglycemia, ketoacidosis, & hypertriacylglycerolemia
  - are due a deficiency of insulin & a relative excess of glucagon

- T2DM has strong genetic component.
- T2DM results from a combination of insulin resistance and dysfunctional β cells.
- Obesity is the most common cause of insulin resistance.
- The metabolic abnormalities in T2DM:
  - are milder than those in T1DM, because of insulin secretion , although not adequate, does restrain ketogenesis
  - Hyperglycemia & hypertriacylglycerolemia
- The long-standing hyperglycemia → chronic diabetic complications (micro- & macro vascular)

Test your knowledge ..!

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

A) FBG

B) HBA1C

C) FFAs

2- Which one of the following is a metabolic effect of insulin:

A) ↑ Lipolysis

B) ↓ Fatty acid oxidation

C) ↑ Glycogenolysis

3- During sorbitol production, consumption of which one of the followings can lead to increased oxidative stress:

A) NADPH

B) aldose reductase

C) Insulin

4- sorbitol is converted to fructose by sorbitol dehydrogenase enzyme that present in :

A) Lens

B) Seminal vesicles

C) Kidney

Answers: 1) B 2) B 3) A 4) B

Biochemistry
Team

If you find any mistake, please contact us =)

Biochemistryteam@gmail.com

Biochemistry team leaders:

Basil AlSuwaine & Manar AlEid

THANK YOU