Metabolic Changes in Diabetes Mellitus

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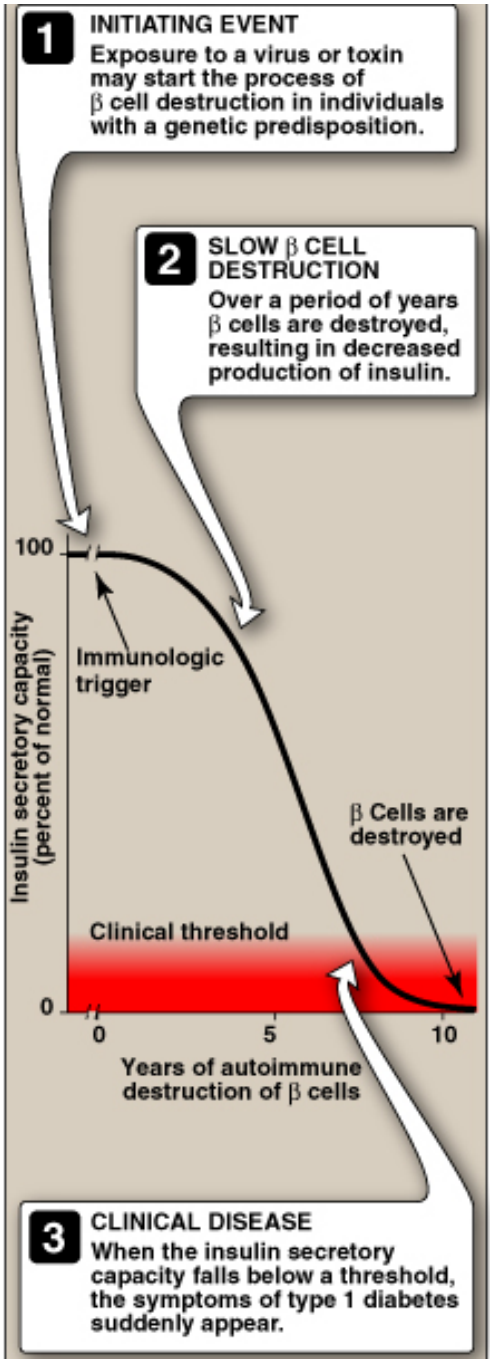
Lecture outlines

- **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**

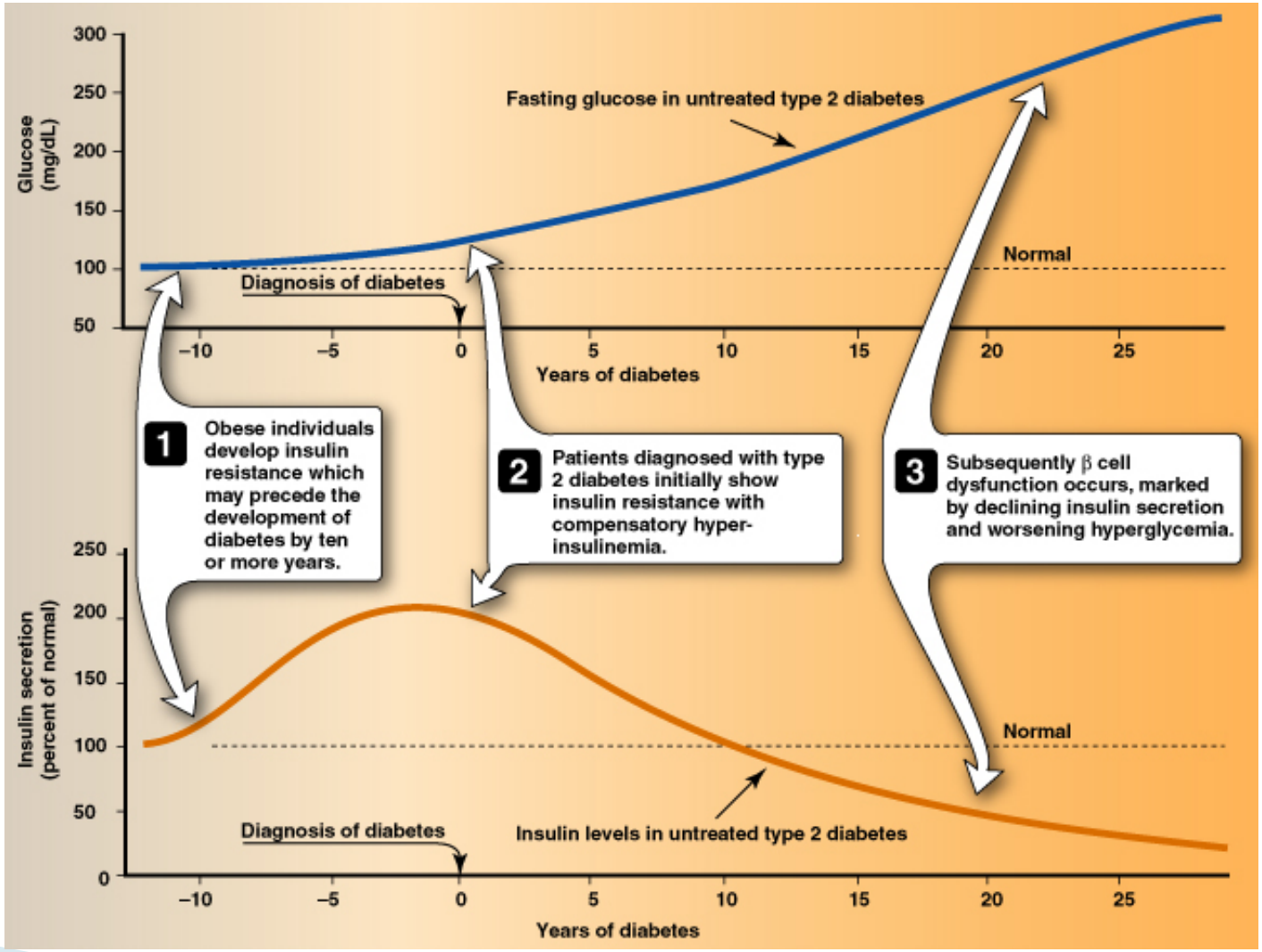
Comparison of type 1 and type 2 DM

	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



Criteria for Diagnosis of DM*

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.

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.
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***American Diabetes Association (ADA), 2010**

HEMOGLOBIN A1C

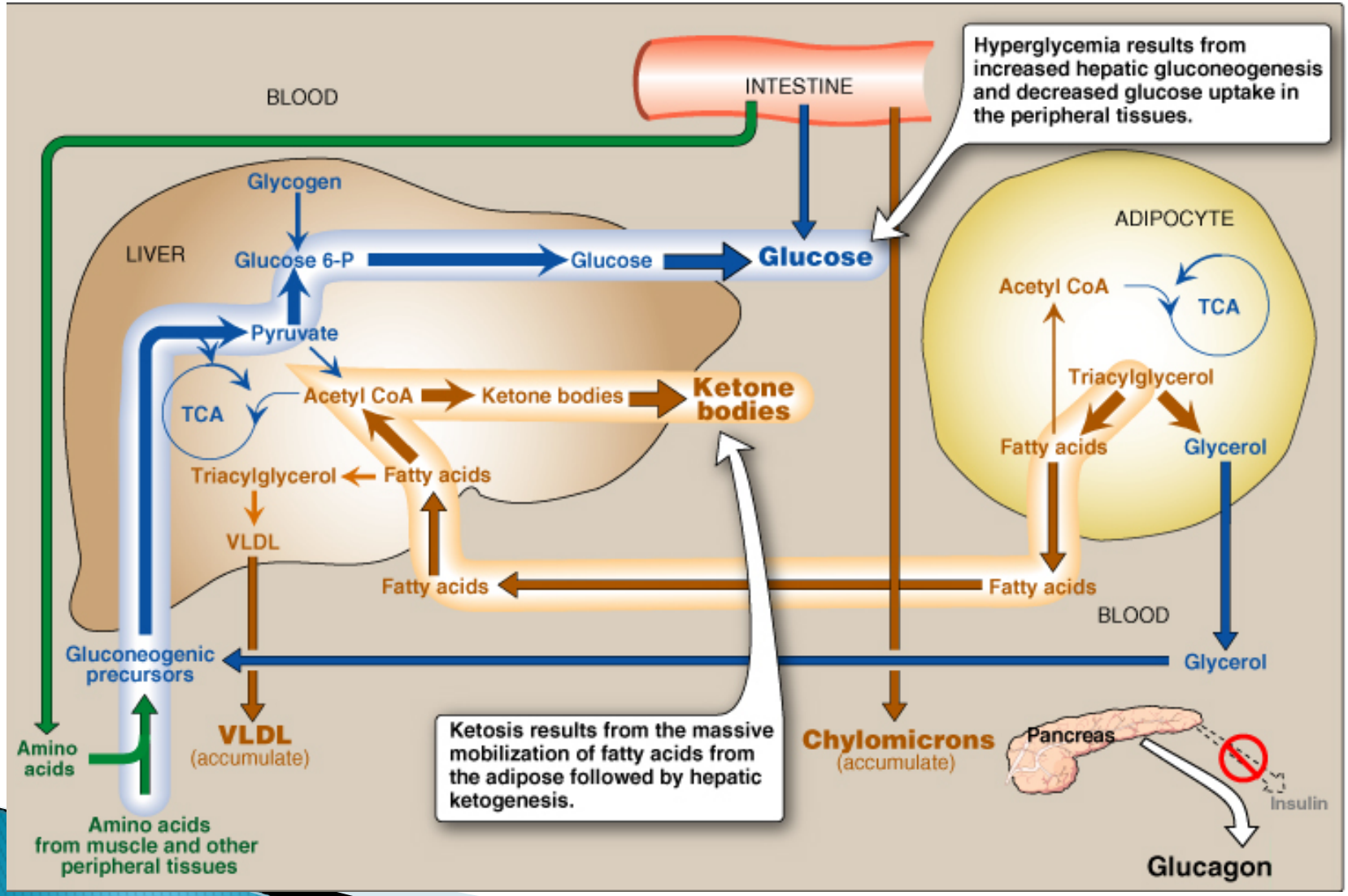
- Hemoglobin A1C (A1C) is the result of non enzymatic covalent glycosylation of hemoglobin
- It is used to estimate glycemic control in the last 1-2 months
- Recently, A1C is recommended for the detection of T2DM
- A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing 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

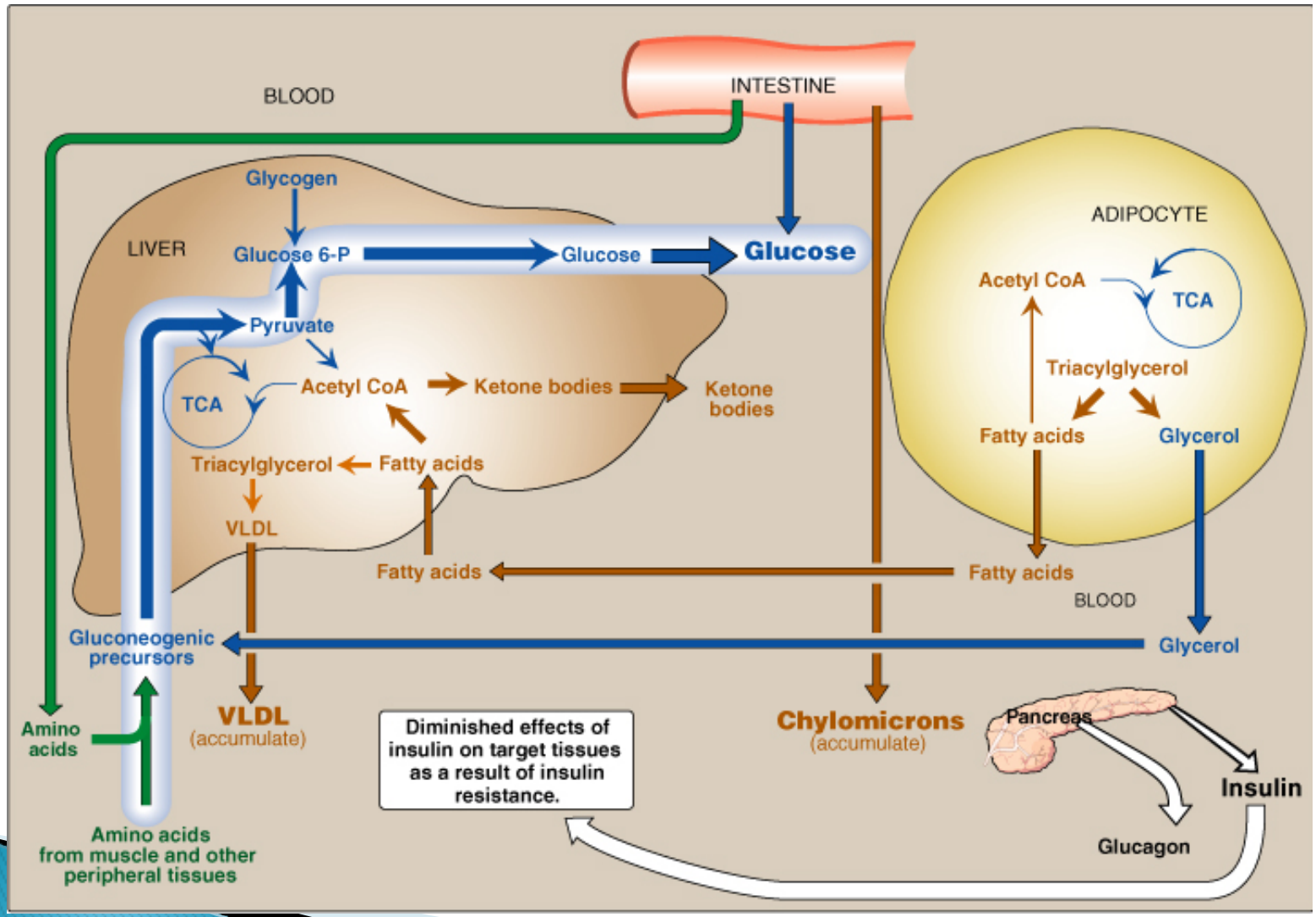
- **Absolute or relative insulin deficiency →**

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

Intertissue Relationship in T1DM



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 Decrease of Peripheral Glucose Uptake

Muscle

↓ Insulin

↓

↓Glucose & amino acid uptake
↑Protein breakdown

↓

↑Plasma glucose
↑Plasma amino acids

Adipose Tissue

↓ Insulin

↓

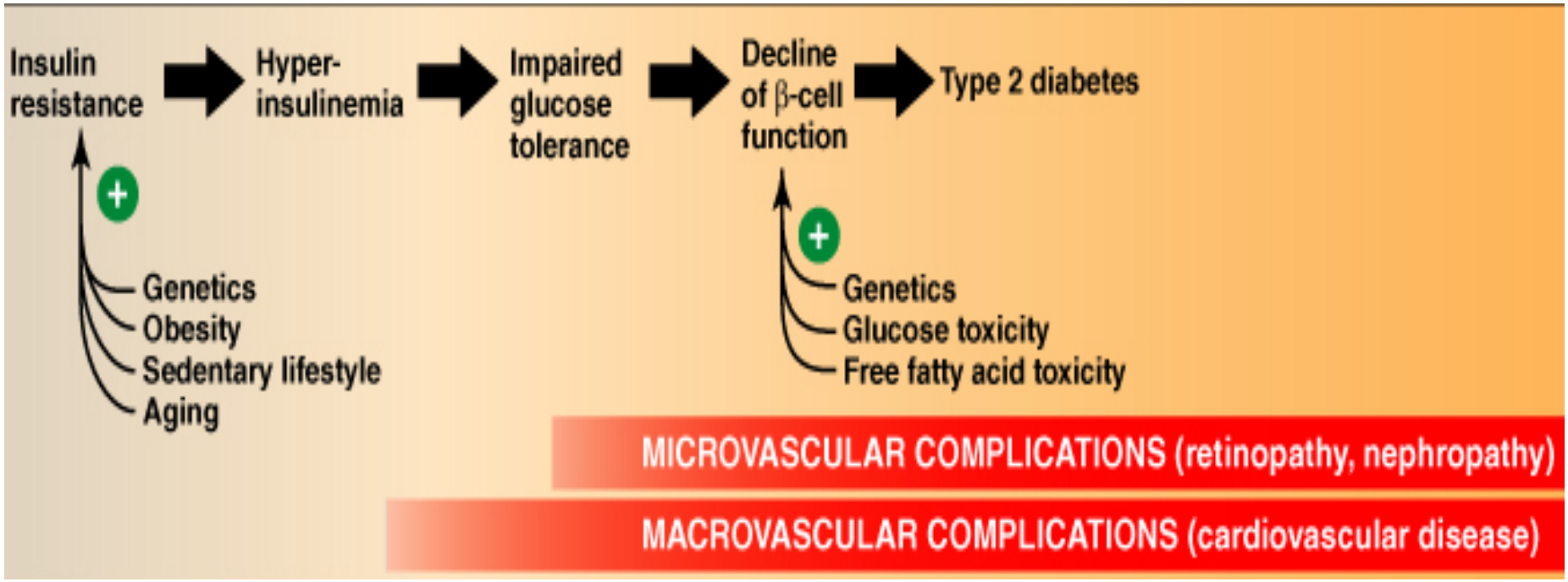
↓ Glucose uptake

↓

↑Plasma glucose

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**

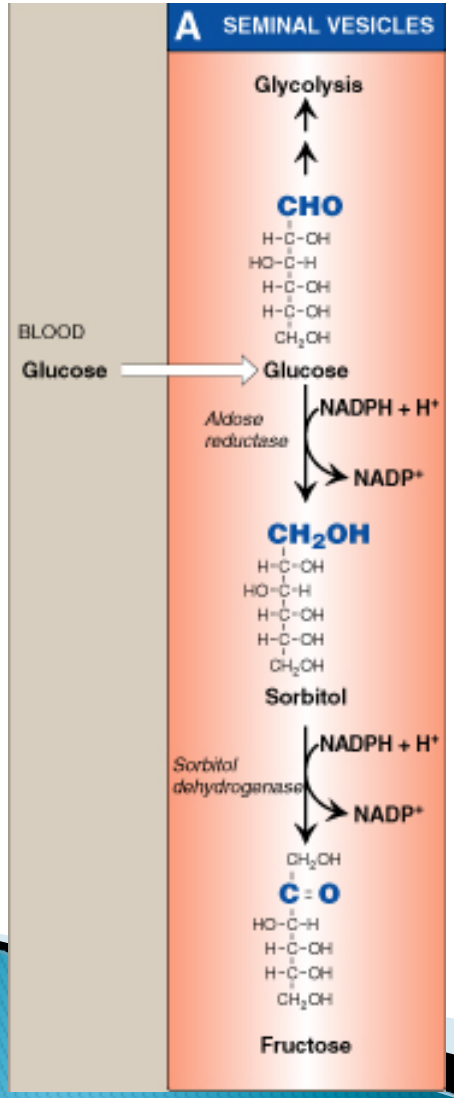
Advanced Glycosylation End Products (AGEs)

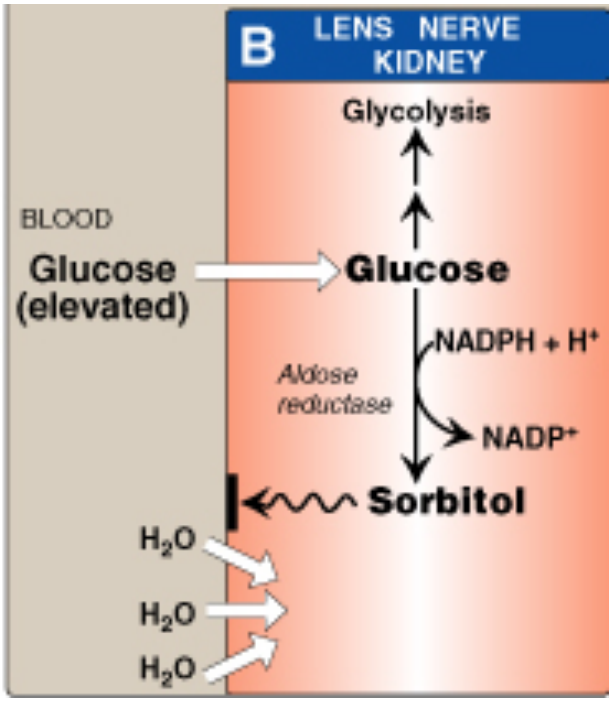
- Chronic hyperglycemia →non-enzymatic combination between excess glucose & amino acids in proteins → formation of AGEs
- AGEs may cross link with collagen → microvascular complications
- The interaction between AGEs and their receptor (RAGE) may generate reactive oxygen species (ROS) → inflammation

Polyol pathway

- 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 Metabolism
Polyol Pathway
A Mechanism for 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:
  - (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

Glomerular hyperfiltration

Microalbuminuria

Proteinuria & ↓ GFR

End-stage renal disease

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

THANK YOU