Metabolic Changes in Diabetes Mellitus

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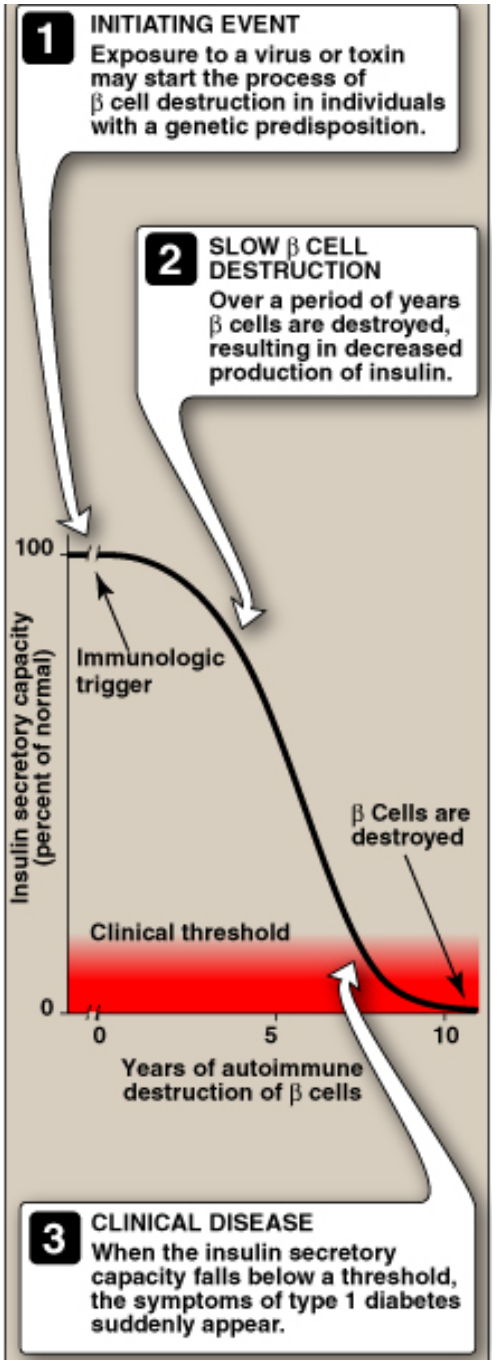
Lecture outlines

- **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**

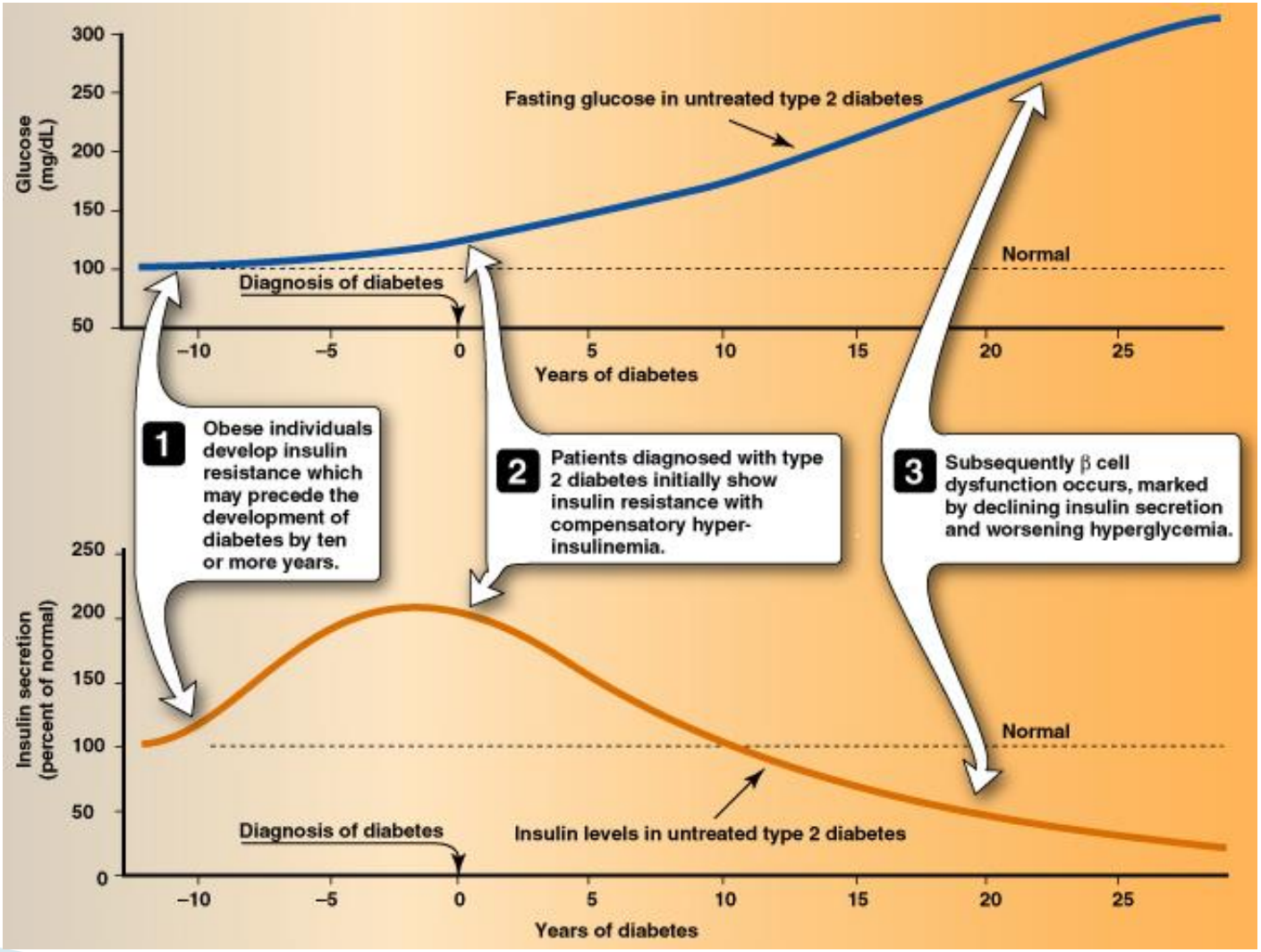
Comparison of type 1 and type 2 DM

	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	< 10 % of diagnosed diabetics	> 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 to absent in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar hyperglycemic state
Response to Oral Hypoglycemic Drugs (OHG)	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, OHG, insulin (may or may not be necessary), reduction of risk factors (weight reduction, smoking cessation, BP control, treatment of dyslipidemia) is essential to therapy

Natural course of T1DM



Progression of T2DM



Criteria for Diagnosis of DM*

Categories of increased risk for diabetes 2016*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–46 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Criteria for the diagnosis of diabetes 2016*

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

***American Diabetes Association (ADA), 2016**

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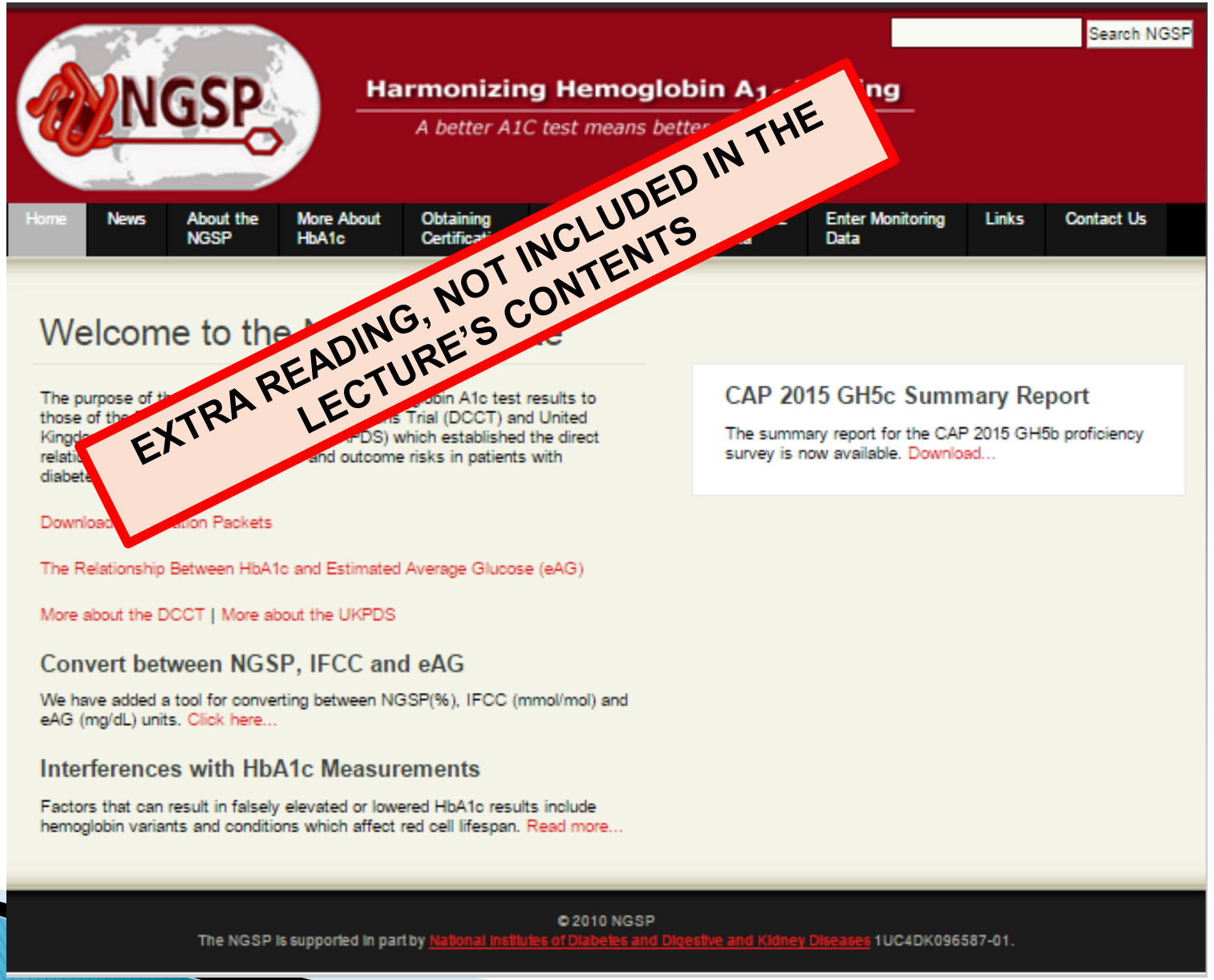
FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; PG: post glucose; OGTT: Oral glucose tolerance test; IGT: Impaired glucose tolerance; A1C: Glycated hemoglobin.

***American Diabetes Association (ADA), 2016**

National Glycohemoglobin Standardization Program (NGSP)



HEMOGLOBIN A1C

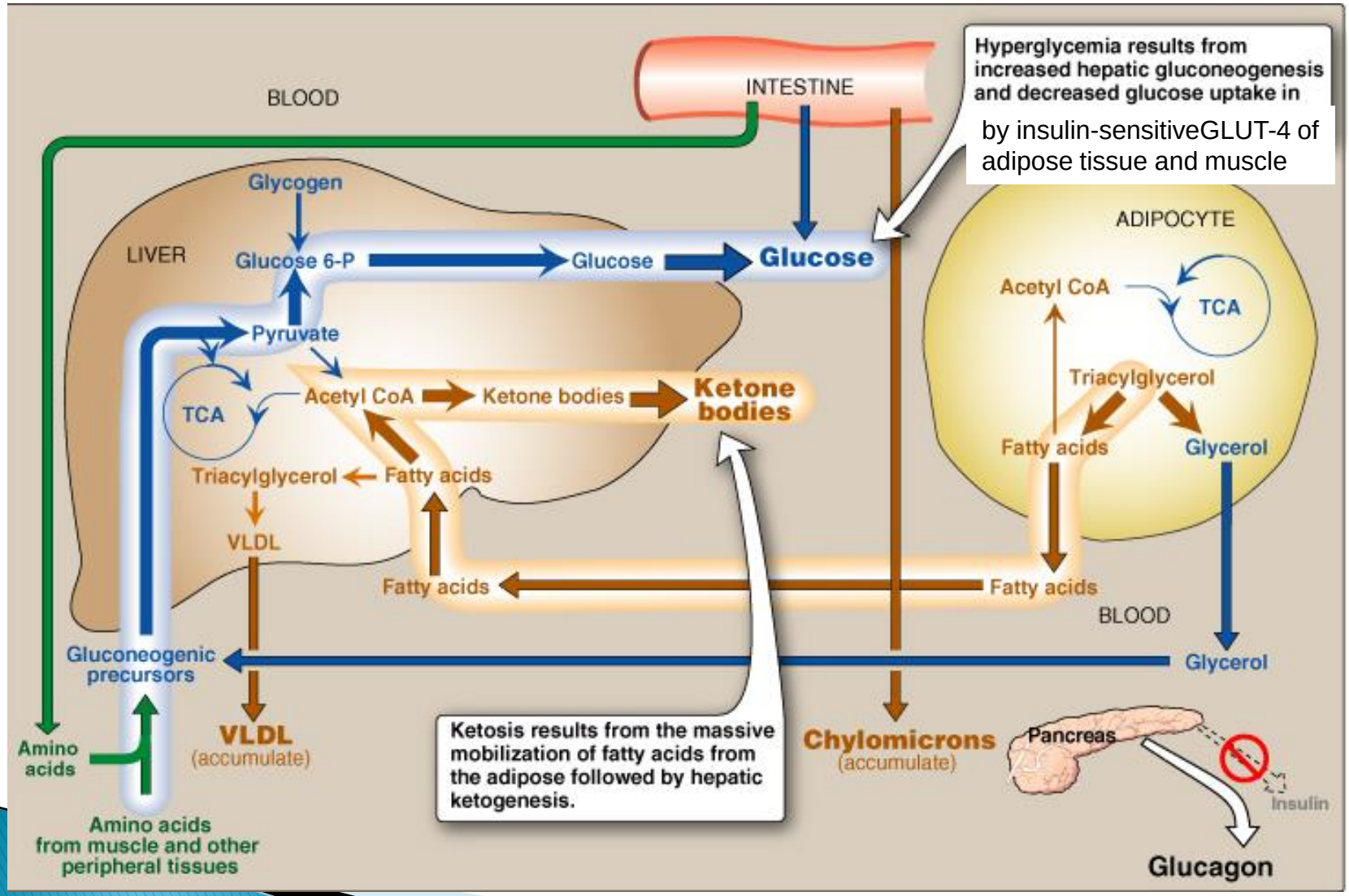
- Hemoglobin A1C (A1C) is the result of non enzymatic covalent glycosylation of hemoglobin
- It is used to estimate glycemic control in the last 1-2 months
- Recently, A1C is recommended for the detection of T2DM
- A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing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

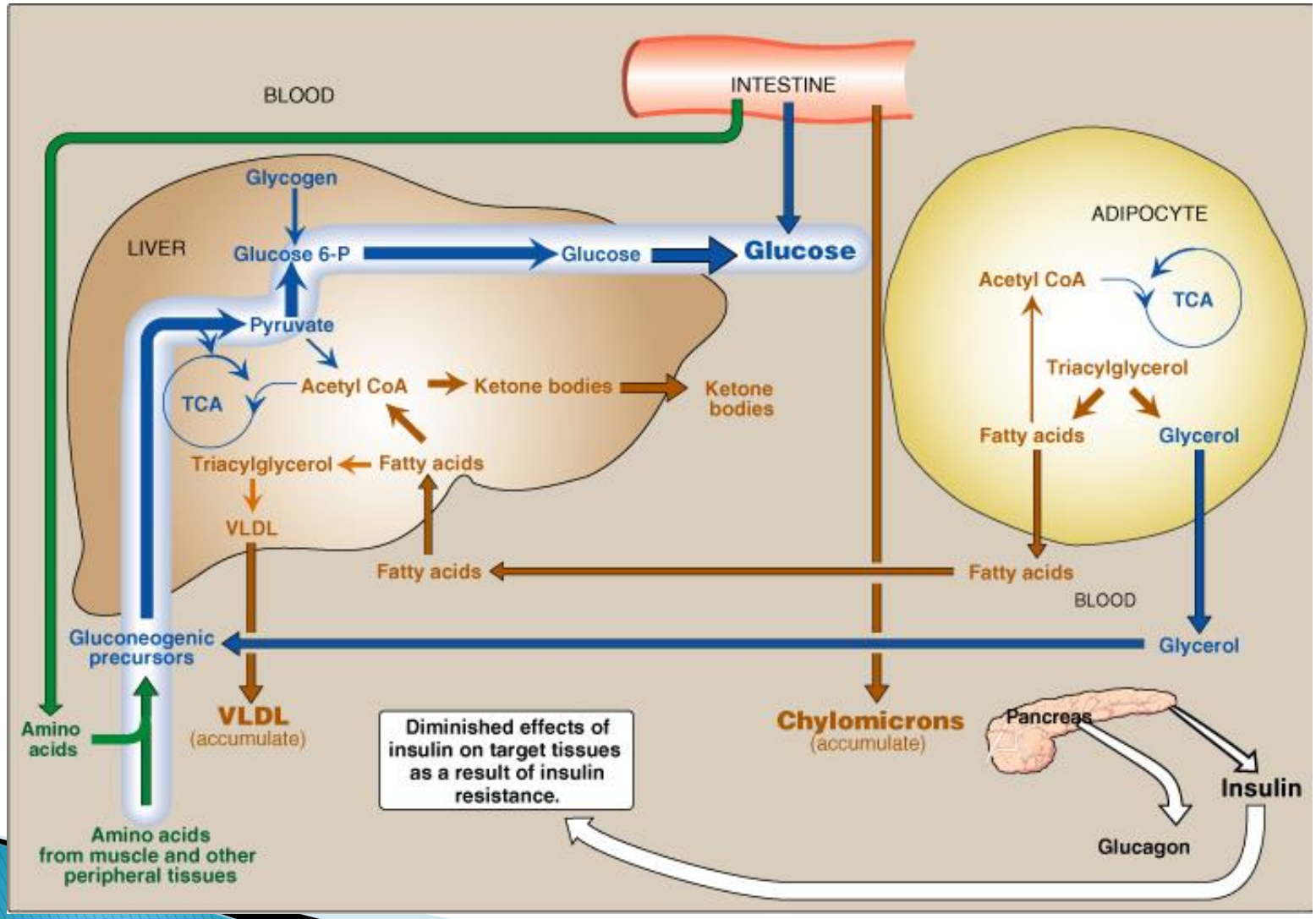
- Absolute or relative insulin deficiency →

1. ↓ Glucose uptake (by muscle & adipose tissue)
2. ↑ Glucose production (from 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 & sk. 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

↓ 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

↓

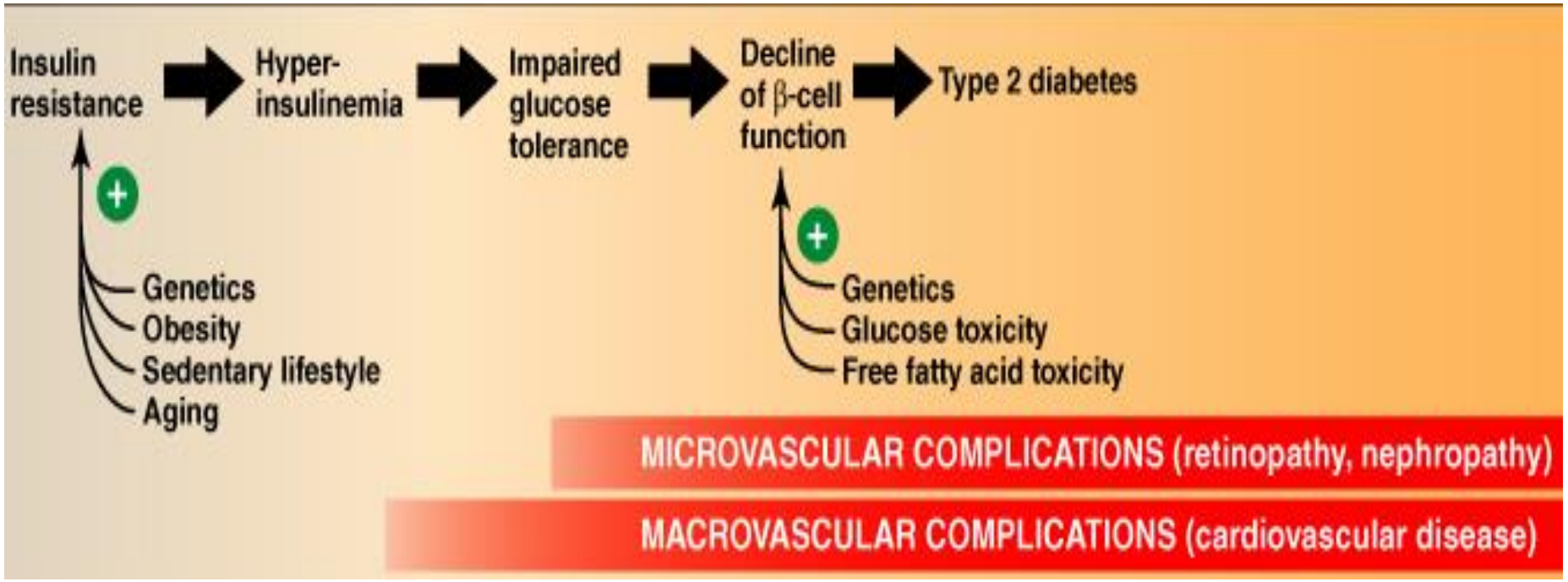
↓ Glucose uptake

↓

↑Plasma glucose

Mechanisms of Diabetic Complications

Typical Progression of T2DM



General Mechanisms for Diabetic Microvascular Complications

Chronic hyperglycemia →

1. ↑ 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

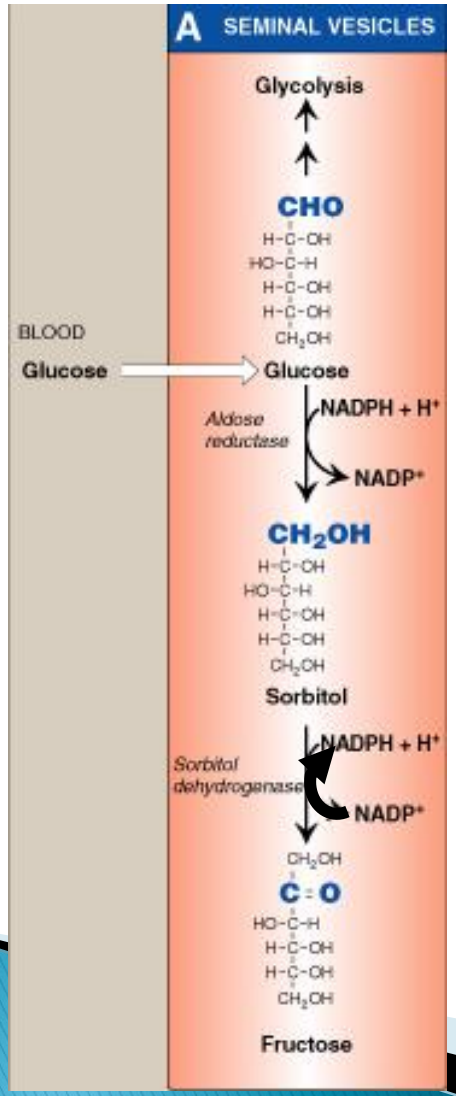
Advanced Glycosylation End Products (AGEs)

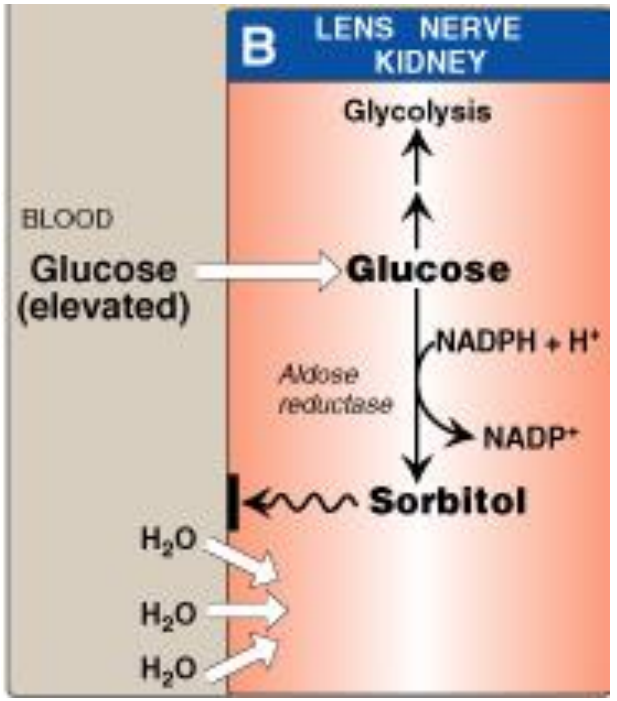
- Chronic hyperglycemia → non-enzymatic combination between excess glucose & amino acids in proteins → formation of AGEs
- AGEs may cross link with collagen → microvascular complications
- The interaction between AGEs and their receptor (RAGE) may generate reactive oxygen species (ROS) → inflammation

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