Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

Metabolic Changes in Diabetes Mellitus

Editing file

Don't Stop when you are Tired.
Stop When You are Done.
- Unknown

OBJECTIVES

By the end of this lecture, the student should be able to understand:

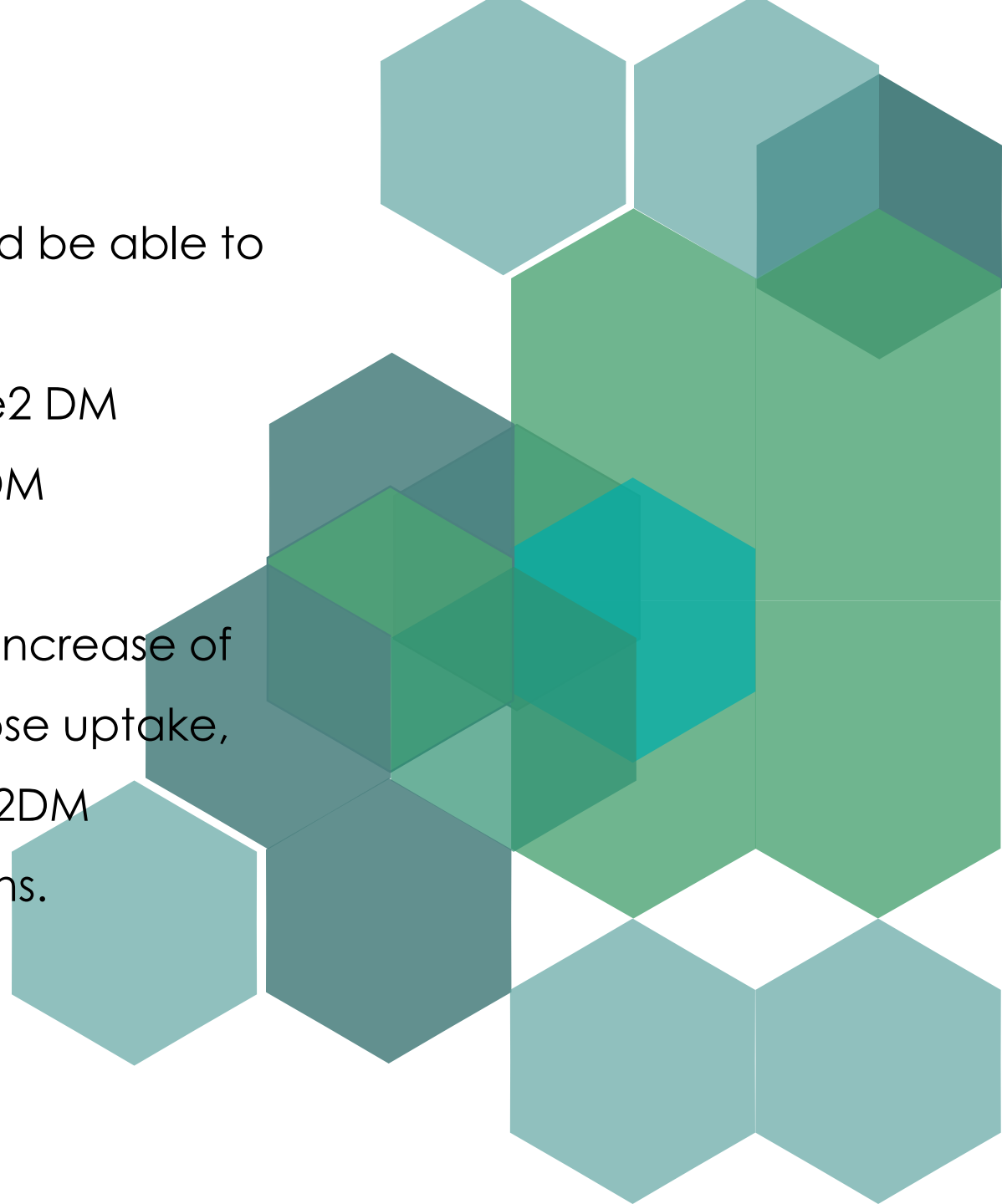
1-The differences between type 1 and type2 DM

2-The natural course of type 1 and type 2 DM

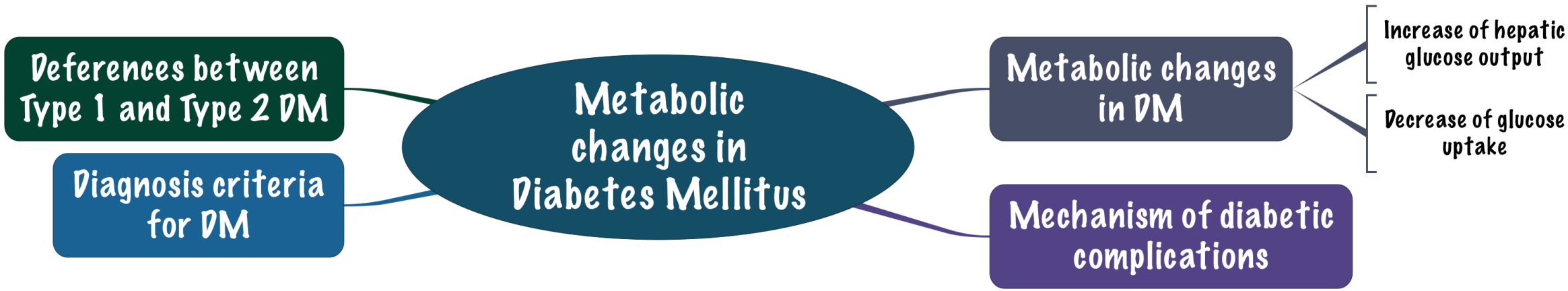
3-The diagnostic criteria for DM

4-The metabolic changes in DM including: increase of hepatic glucose output, decrease of glucose uptake, and inter-organ relationship in T1DM and T2DM

5-The mechanisms of diabetic complications.



Overview


Deferences between Type 1 and Type 2 DM
Diagnosis criteria for DM
Metabolic changes in Diabetes Mellitus
Metabolic changes in DM
Increase of hepatic glucose output
Decrease of glucose uptake
Mechanism of diabetic complications

Comparison of type 1 and type 2 DM

Definition of diabetes:

1-Diabetes is an endocrine disease or a problem due to absolute or relative deficiency of insulin.

2-It is a combination of chronic diseases with underline hyperglycaemia because there are chronic complications associated with diabetes but the main feature is hyperglycaemia

	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

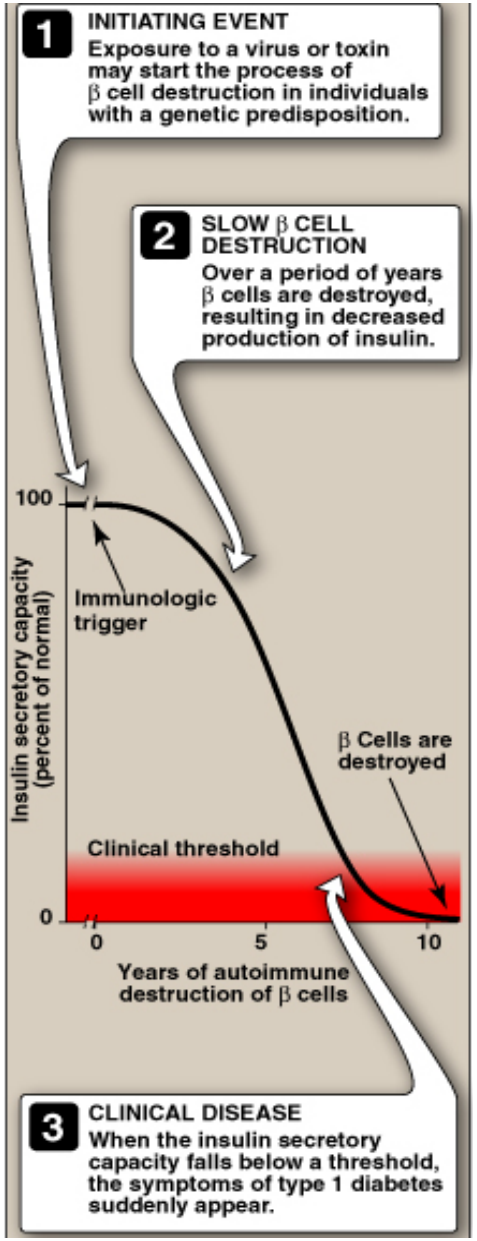
Usually people don't know that they have type 2 and they discover it by coincidence

In the beginning of type 2 the level of insulin will be high because of compensatory mechanism, but after longer duration the level will goes down because of dysfunctional beta cells, While in type 1 it will absent from the beginning Because of beta cells destruction.

Hyperosmolar hyperglycemic state = Coma

Natural course of T1DM

- these people are genetically redisposed to autoimmune disease.
- they has to be an initiating even like viral infection (immunologic trigger) and this trigger cause T-cell infiltration into islets of Langerhans and they start to attack beta cells which called Insulitis.
- Then the insulin level will decreases gradually but you will not see any symptoms because this level is still sufficient to maintain glucose level.
- After when 80%-90% of beta cells have died then you will able to see the clinical symptoms, and when the symptoms appears the progression will be fast.
- So, if you see the clinical symptoms that's mean the remaining insulin secretory capacity is only 10%-20% (the clinical threshold).
- We call it absolute insulin deficiency because it doesn't produce insulin at all.

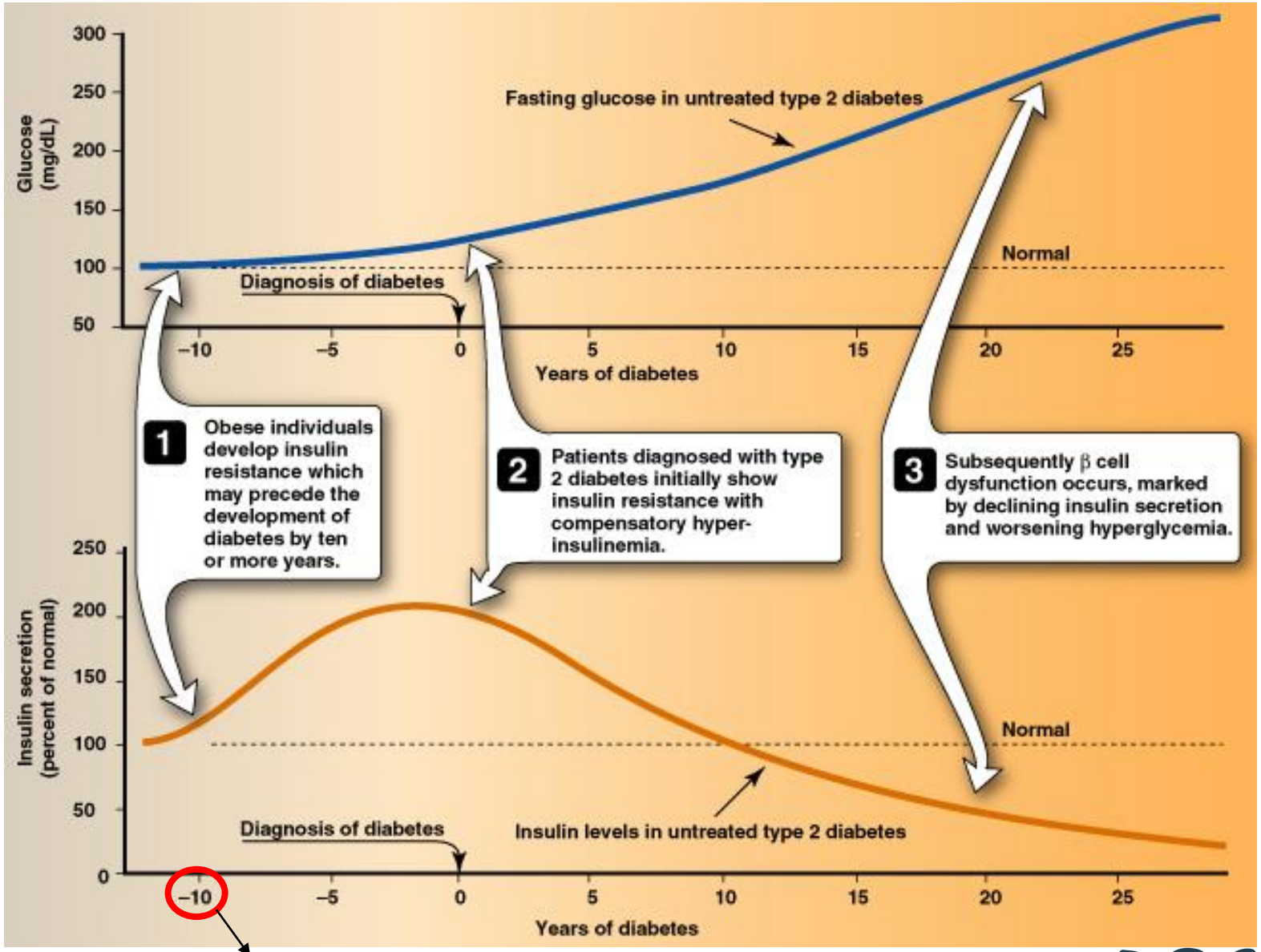


Progression of T2DM

1. To maintain this high glucose level in insulin resistance patients the body needs more insulin as compensation.

2. after time the insulin will not be sufficient to control the glucose level and it will raise up at this time you will diagnose type 2 DM.

3. If you not treat the patient the high level of glucose will start act as a toxic and it will cause dysfunction of beta cells, that will reduce the level of insulin, But even when the disease progressed there will be some amount of insulin production, and this small amount of insulin is enough to stop Ketone bodies formation, that's why diabetes ketoacidosis is not a complication of type 2 DM.



10 years before the diagnosis

Criteria for Diagnosis of DM

Categories of increased risk for diabetes* (Pre-diabetic)

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.

These people can delay the disease onset by modifying their life style.

American Diabetes Association (ADA), 2016

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.
Reprinted with permission from: American Diabetes Association. Standards of Medical Care in Diabetes Care 2010; 33:S11.

HEMOGLOBIN A1C & Metabolic Effects of Diabetes Mellitus

❖ Hemoglobin A1C :

Hemoglobin A1C:	is the result of non enzymatic covalent glycosylation of hemoglobin.
Used for	• It is used to estimate glycemic control in the last 1-2 months. Because the life span of RBCs. • A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes. But to monitor the progression of the disease or treatment A1C is more effective, because it tells you about what happened in long prided of time.
notes	• 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). • Recently, A1C is recommended for the detection of T2DM.

Metabolic Effects of Diabetes Mellitus

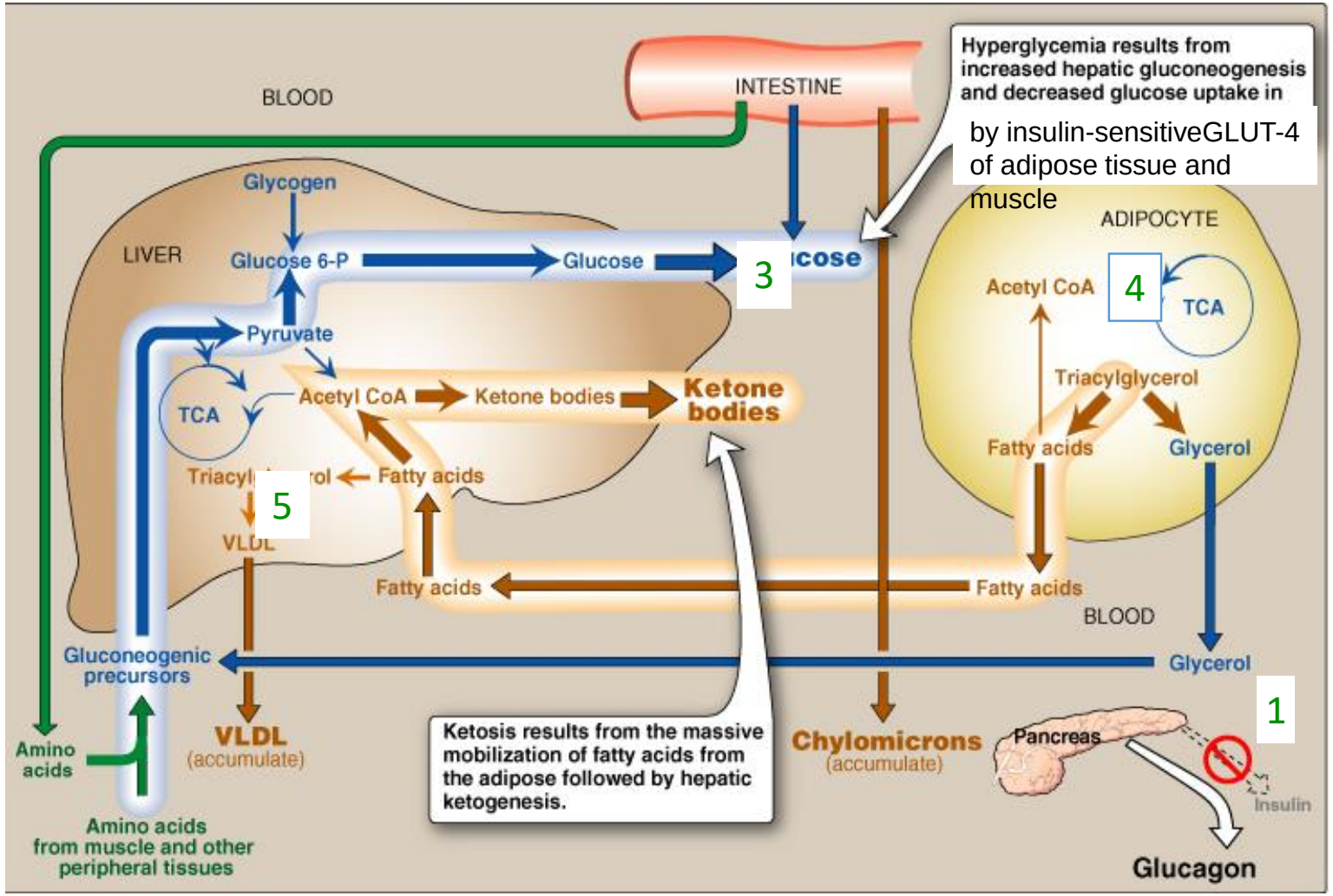
❖ Metabolic Effects of Diabetes Mellitus :

Absolute or relative insulin deficiency → absolute as in T1DM(complete lack of insulin activity),relative as in T2DM(about 10% of insulin activity is conserved .

- ↓ Glucose uptake (by muscle & adipose tissue)
- ↑ Glucose production (from liver). By gluconeogenesis

Intertissue Relationship in T1DM

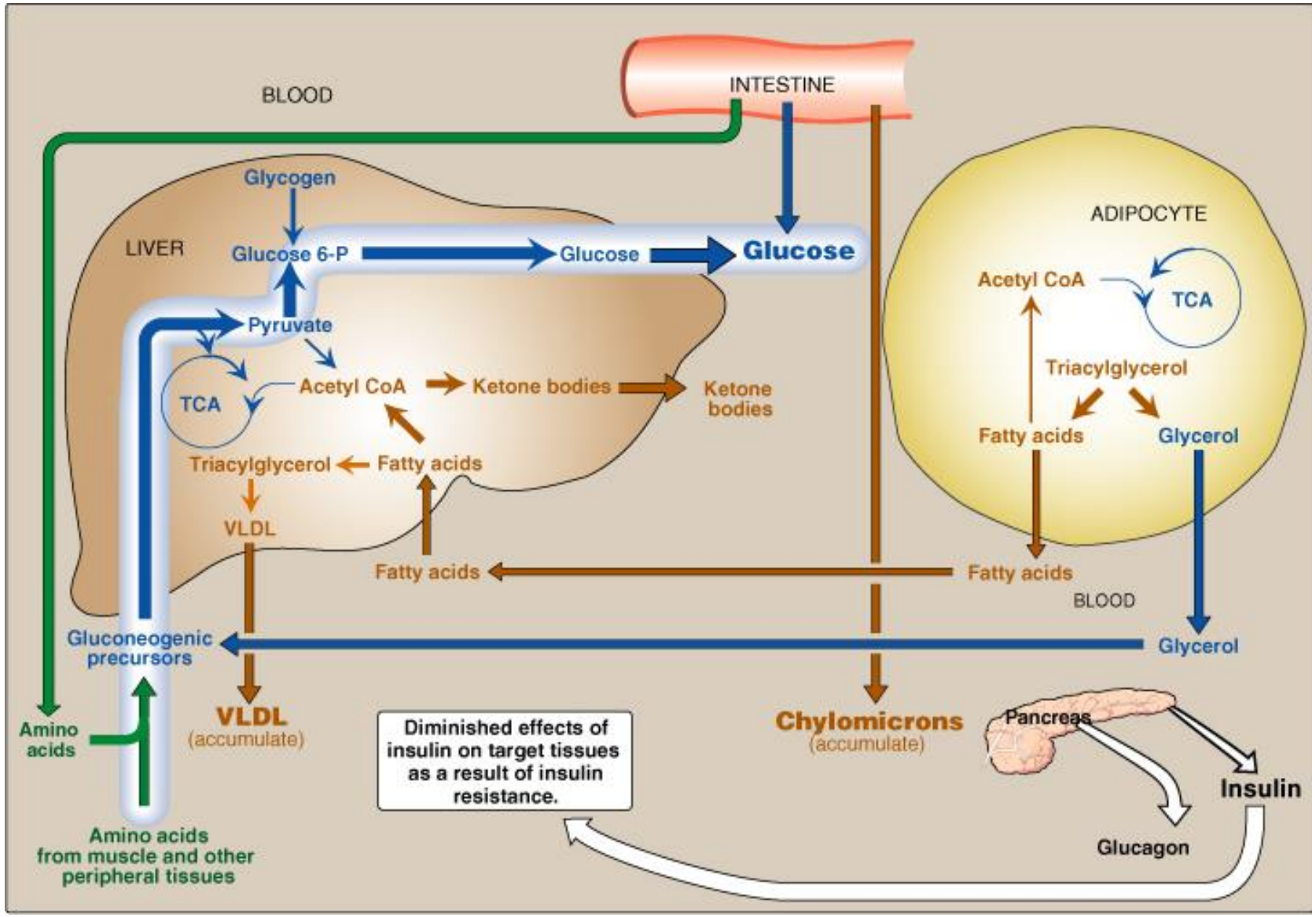
1. 1- When you eat normally insulin will be secreted but in type 1 DM There is no insulin secretion, instead of insulin glucagon will secreted.
2. 2- the amino acid will be gluconeogenic precursors (they will be used in gluconeogenesis).
3. 3- you will have a lot of glucose from food and gluconeogenesis.
4. 4- in this situation and because of there is No uptake of glucose due to lack of insulin your adipocyte will break down TAGs into glycerol (which used in gluconeogenesis), and fatty acid.
5. 5- the fatty acid will goes into liver where they synthesize Ketone bodies, also they participate in the production of VLDL. So the excess amount fatty acids will cause excessive Ketone bodies formation which called Ketosis.
6. - So you will have Hyperglycemia, dyslipidemia and Ketosis in type 1 diabetes.



Intertissue Relationship in T2DM

1. The same mechanism in type 2 BUT, because we have some insulin releasing that will uptake a little amount of glucose inside the muscles and adipose tissues, and that's why the amount of fatty acid that produced here is not so much as the type 1 DM, And that's why type 2 DM patients are obese while type 1 are not!!

2. There is Ketone bodies formation but will not cause Ketosis because their amount is not very high



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). Much worse in type 1.

Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

Mechanisms of Increase Hepatic Glucose Output & Decrease of Peripheral Glucose Uptake:

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

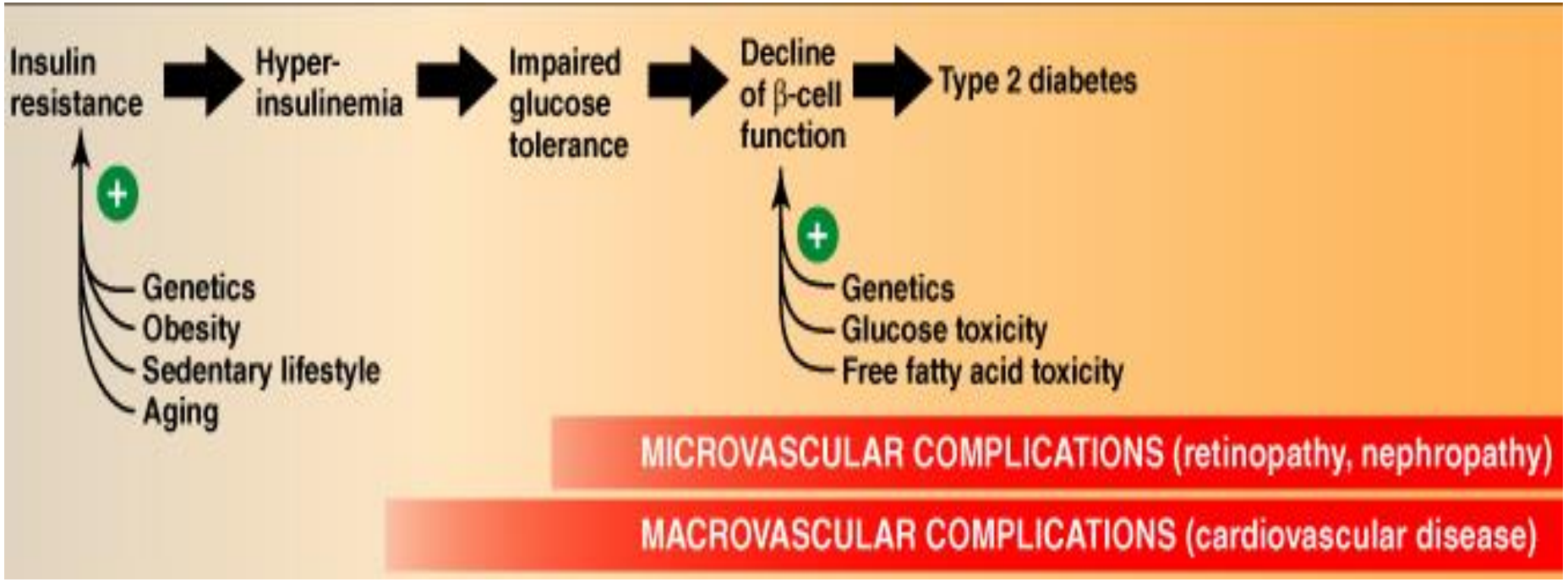
↓ Insulin

↓ Glucose uptake

↑Plasma glucose

Mechanisms of Diabetic Complications

❖ Typical Progression of T2DM



And nephropathy

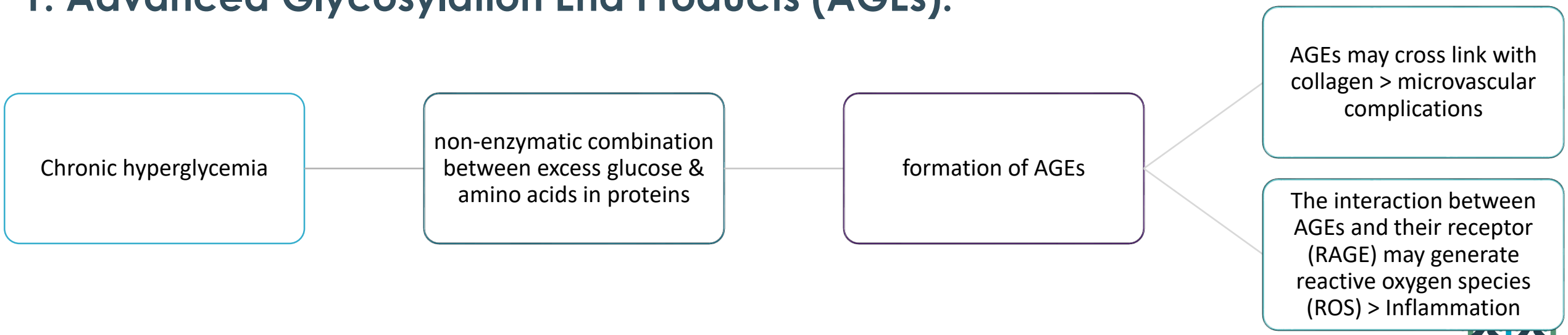
General Mechanisms for Diabetic Microvascular Complications

❖ General Mechanisms for Diabetic Microvascular Complications:

In chronic hyperglycemia :

1. ↑ Advanced Glycation End products (AGEs) of essential cellular proteins → cellular defects protein get glycated Like hemoglobin A1C and these glycated proteins may cause inflammation
2. ↑Intracellular sorbitol → ↑ cell osmolality → cellular swelling. Alcoholic form of glucose, which is osmotically active so it brings the fluids inside the cells and causes cellular swelling
3. ↑ Reactive Oxygen Species (ROS) → oxidative stress → cell damage

1. Advanced Glycosylation End Products (AGEs):



General Mechanisms for Diabetic Microvascular Complications

2. Polyol pathway:

Pathway of sorbitol production

- 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:

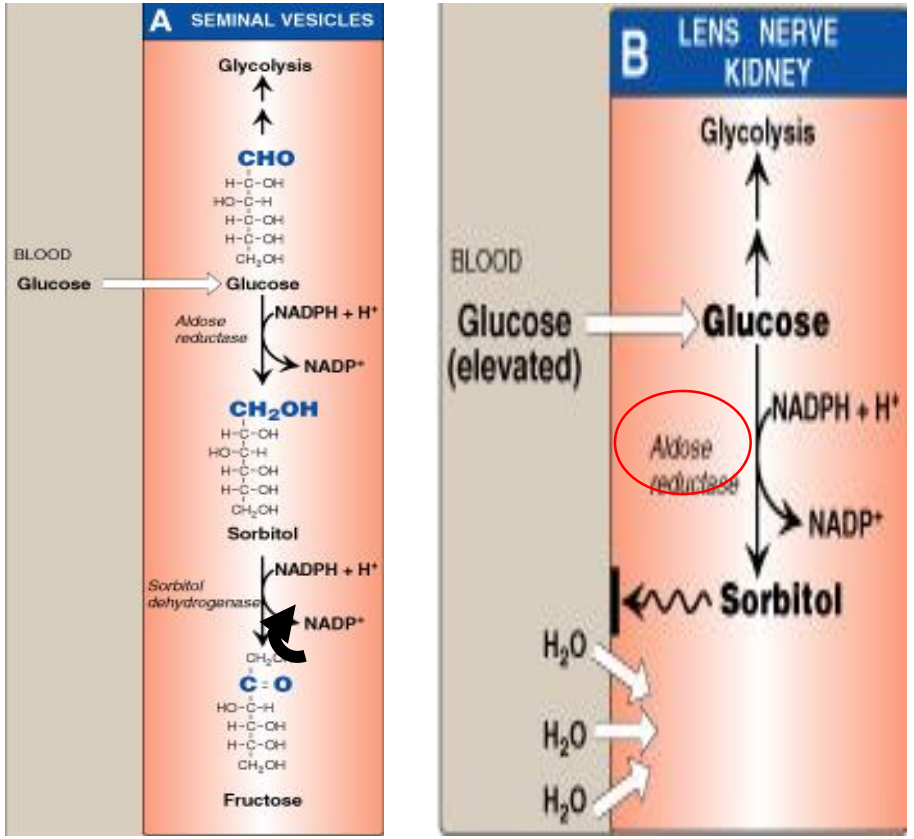
i. During sorbitol production, consumption of NADPH → oxidative stress.

ii. Sorbitol accumulation:

- Increase the intracellular osmotic pressure → osmotic drag of fluid from extracellular space → cell swelling
- Alteration in the activity of PKC (Protein kinase C) → altered VEGF (Vascular Endothelial Growth Factor) activity→ altered vascular permeability

Some tissues like ovaries can convert sorbitol into Fructose because they have sorbitol dehydrogenase, but most of the tissues don't have this enzymes

Sorbitol Formation & Metabolism



Conversion of Sorbitol into Fructose

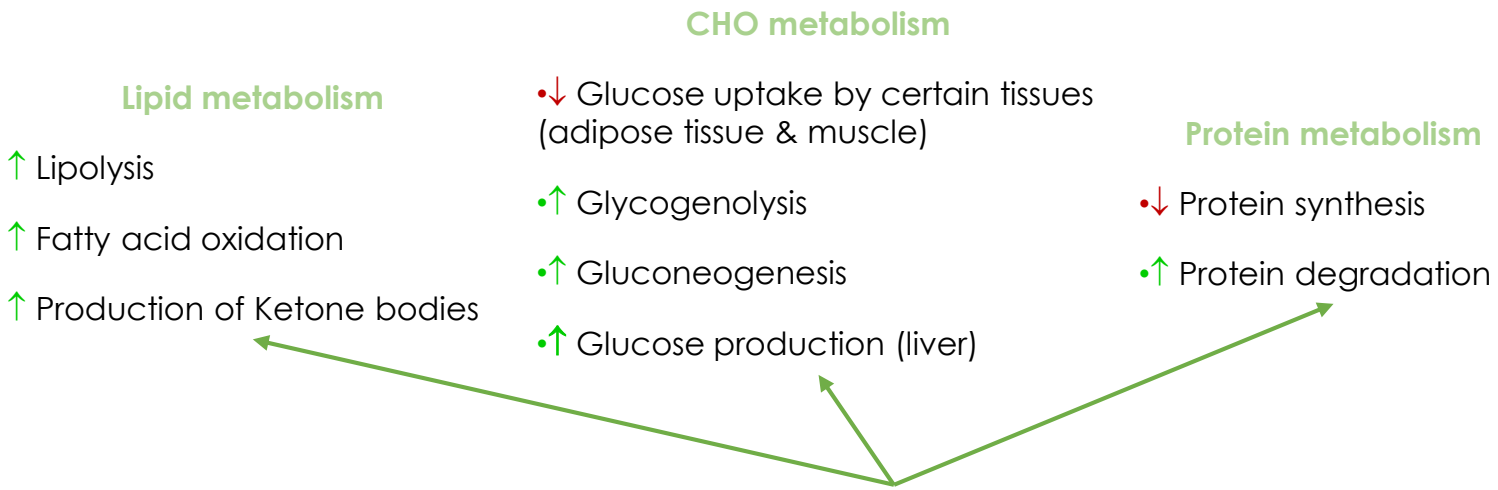
Microvascular Complications :

1.Diabetic Retinopathy:	2.Diabetic Neuropathy:	3.Diabetic Nephropathy:
• 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 and severity also 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	• 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	• 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

Summary



Major Metabolic changes in DM

Criteria for Diagnosis of DM

	Increased risk for diabetes	Diabetes mellitus
FPG	100-125 mg/dl 5.6-6.9 mmol/L	= or >126 mg = or >7 mmol/L
2-h PG on the 75g OGTT	140-199 mg/dl 7.8-11 mmol/L	= or >200 mg = or > 11.1 mmol/L
HbA1C	5.7-6.4 %	> 6.5 %

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)

QUIZ

Q1 : Which one of the following metabolic changes is correct in Diabetes Mellitus?

A. Increased Protein synthesis
B. Increased Protein degradation
C. Increased Glucose Uptake
D. Decreased Protein degradation

Q2 : Which one of the following may cross link with AGEs?

A. Glucose
B. Proteins
C. Keratin
D. Collagen

Q3 : Which one of the following is a complication of sorbitol accumulation?

A. Decreased gluconeogenesis
B. Retinopathy
C. Alteration of vascular permeability
D. Insulin resistance

Q4 : Which one of the following is the earliest clinical finding of diabetic nephropathy?

A. Nephrotic syndrome
B. Microalbuminuria
C. Glucosuria
D. Proteinuria

Q5 : Microalbuminuria progresses into which of the following?

A. Nephritic syndrome
B. Pyelonephritis
C. Glucosuria
D. Decreased GFR

Q6 : Which one of the following is a macrovascular complication?

A. Nephropathy
B. Retinopathy
C. Cardiovascular diseases
D. Neuropathy

QUIZ

Q7 : 2 year old boy came to your clinic with his parents.
They say that he has been needing a lot of diapers changed lately because of his frequent passing.
The mother also noticed that there is a strong fruity smell coming from his urine.

A) How can glucose hepatic output increase in diabetes mellitus ?

Decrease in insulin leads to decreased inhibition of glucagon secretion which in turn increases glucagon levels, causing a negative feedback of increased gluconeogenesis and glycogenolysis in the liver
Thus leading to increased plasma glucose.

B) Mention 3 complications that are associated with diabetes mellitus.

1. Diabetic Nephropathy
2. Diabetic Neuropathy
3. Diabetic Retinopathy

C) What are the factors that induce insulin resistance?

1. Genetics
2. Obesity
3. Sedentary lifestyle
4. Aging

D) How are Advanced glycosylation end products (AGEs) formed?

Chronic hyperglycemia leads to non-enzymetic combination between excess glucose and amino acids which leads to formation of AGEs

Suggestions and recommendations

1) B 2) D 3) C 4) B 5) D 6) C

Biochemistry Team 436

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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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