Biochemistry Bandits 434

METABOLIC CHANGES IN DIABETES MELLITUS

OBJECTIVES:

- Background
- Diagnostic criteria for DM
- Metabolic changes in DM
- Mechanisms of diabetic complications

Abbreviations:

DM diabetes mellitus
T1DM type1 Diabetes mellitus
T2DM type 2diabetes mellitus
FPG fasting plasma glucose
OGTT oral glucose tolerance test
A1C glycated hemoglobin
VEGF vascular endothelial growth factor

❖ **Important** ❖ Extra ❖ Biochemistry Edit

ENDOCRINE BLOCK

COMPARISON OF TYPE 1 AND TYPE 2 DM

	DM type 1	DM type 2
Age of onset	Childhood	Adult
Symptoms develop	Rapidly	Gradually
Defect & deficiency	Destroy β cells	No enough insulin or insulin resistance
Ketosis	Common	Rare
Plasma insulin	Low or absent	Reduce gradually Early high – late low
Acute complication	Ketoacidosis	Hyperosmolar coma
Genetic predisposition	Moderate	Very strong
Using of oral hypoglycemic	No response	Response
Treatment	Insulin	Diet, exercise, oral hypoglycemic, insulin

CRITERIA FOR DIAGNOSIS OF DM

Increased risk of DM

- FPG (5.6-6.9) mmol/L
- OGTT (7.8-11) mmol/L
- A1c (5.7-6.4)%

To convert from mmol/L to mg/dl use this equation (mmol/L X 1 8 = mg/dl)
This is only true for glucose, since it depends on the molecular W. of each substance.

Diagnosis of DM

- FPG > 7 mmol/L
- OGTT > 11.1 mmol/L
- A1c > 6.5%
- Random plasma glucose > 11.1 mmol/L

+ Hyperglycemia symptoms

HEMOGLOBIN A1C

-Hemoglobin A1c (A1C) is the result of non enzymatic covalent glycosylation of hemoglobin
-Assays for A1C has to be standardized according to the National Glycohemoglobin Standardization Program (NGSP).

USES

A1C is recommended for the detection of T2DM

estimate glycemic control in the last 1-2 months

A1C values also correlate with the prevalence of retinopathy

A1C and FPG were found to be similarly effective in diagnosing diabetes.

METABOLIC EFFECTS OF DM

Absolute"TYPE 1" or relative"TYPE 2" insulin deficiency

Multiple metabolic effects		
CHO metabolism	**Lipid metabolism**	**Protein metabolism**
•↓ Glucose uptake by certain tissues (adipose tissue & muscle) •↑ Glycogenolysis •↑ Gluconeogenesis	•↑ Lipolysis •↑ Fatty acid oxidation •↑ Production of Ketone bodies (more in DM type 1)	•↓ Protein synthesis •↑ Protein degradation

INCREASE PLASMA GLUCOSE

Mechanisms of Increase Hepatic Glucose Output

Mechanisms of Decrease of Peripheral Glucose Uptake

Liver
- ↓ Insulin↑glucagon
- ↑Gluconeogenesis & glycogenolysis
- ↑ Plasma glucose

Muscles
- ↓ Insulin
- ↓ Glucose & amino acid uptake
  ↑Protein breakdown
- ↑ Plasma glucosem ↑Plasma amino acids

Adipose Tissue
- ↓ Insulin
- ↓ Glucose uptake
- ↑ Plasma glucose

HYPERGLYCEMIA & GLYCOSYLATION

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

COMPLICATIONS OF DM

- macrovascular
  - CVS disease
- microvascular
  - neuropathy
  - retinopathy

1.POLYOL PATHWAY

When glucose is unused, glucose is metabolized to sorbitol within the cells by aldose reductase via the polyol pathway.

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

2.Diabetic Retinopathy

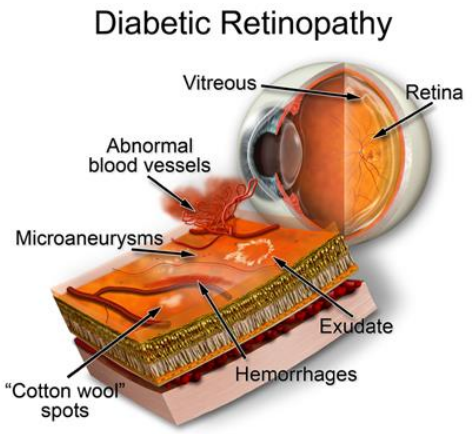
A progressive microvascular complication of DM, affecting the retina of the eye

A major cause of morbidity 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



CONT' COMPLICATIONS OF DM

3.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*

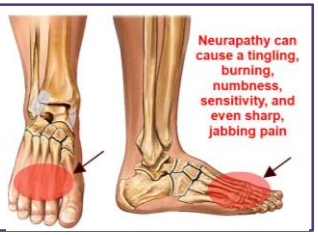
Extra: Diabetic nephropathy may be diffuse or nodular (Kimmelstiel-Wilson lesion). The early stages cause an elevated glomerular filtration rate with enlarged kidneys, but the principal feature of diabetic nephropathy is proteinuria. This develops insidiously, starting as intermittent microalbuminuria before progressing to constant proteinuria and occasionally nephrotic syndrome.

4. Diabetic Neuropathy

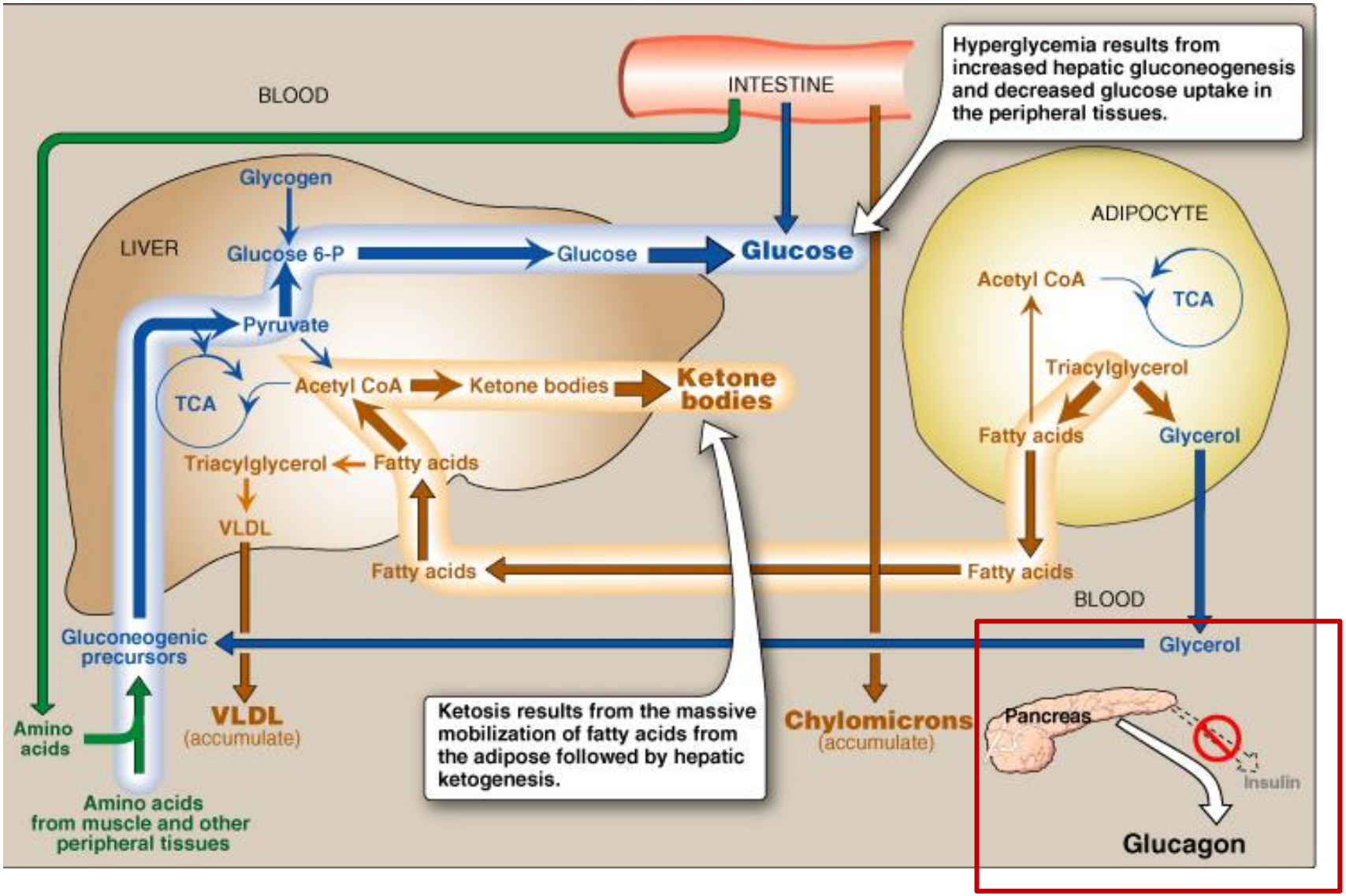
Loss of both myelinated and unmyelinated nerve fibers

Occurs in both type 1 & type 2 DM

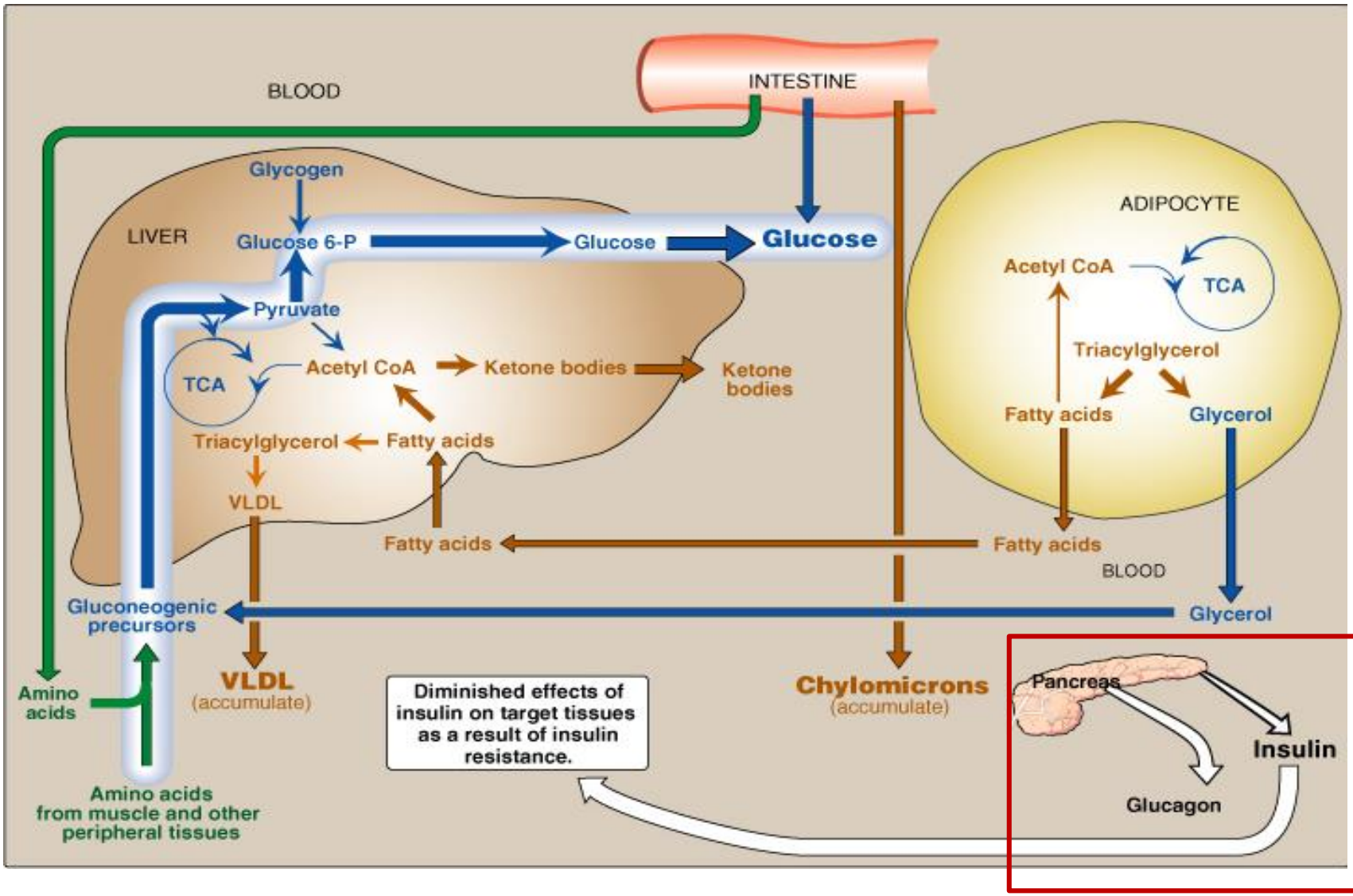
It correlates with the duration of DM & with glycemic control



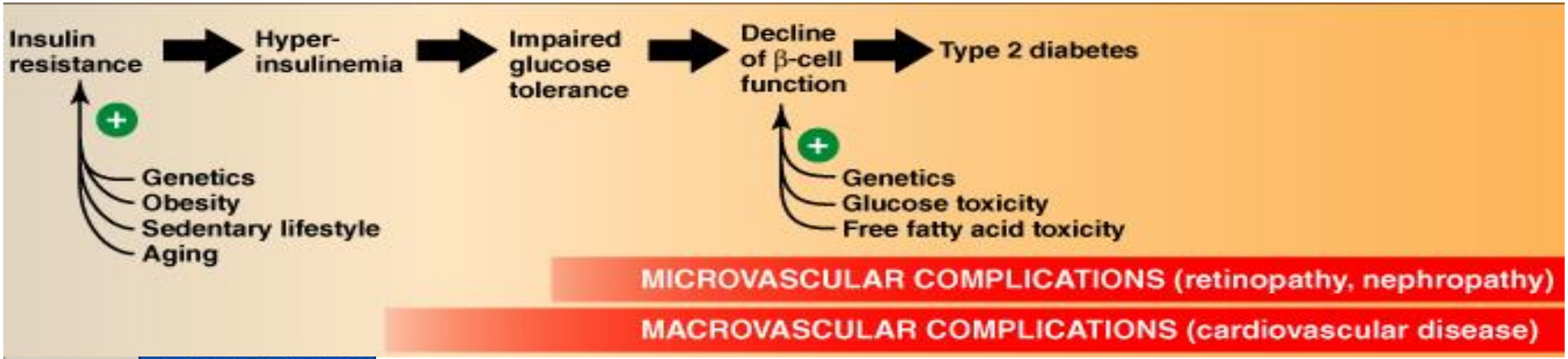
INTERTISSUE RELATIONSHIP IN T1DM



INTERTISSUE RELATIONSHIP IN T2DM

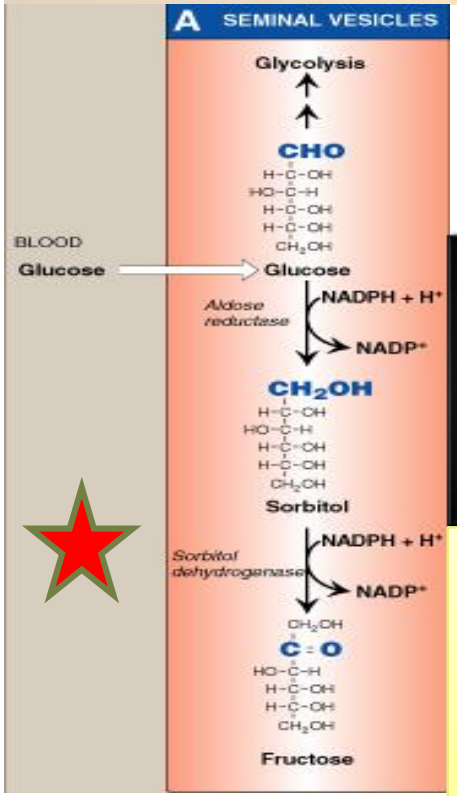


TYPICAL PROGRESSION OF T2DM



SORBITOL METABOLISM

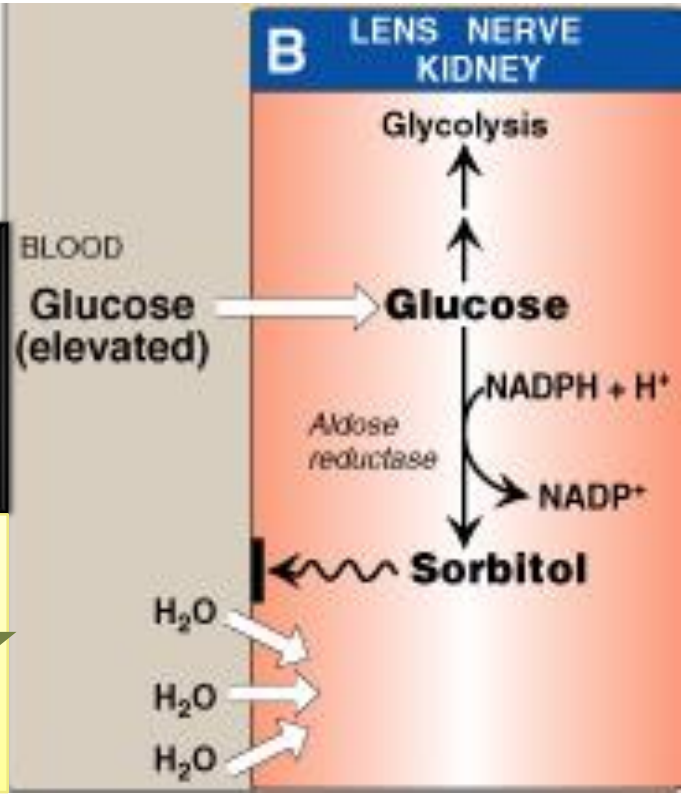
A MECHANISM FOR DIABETIC COMPLICATIONS

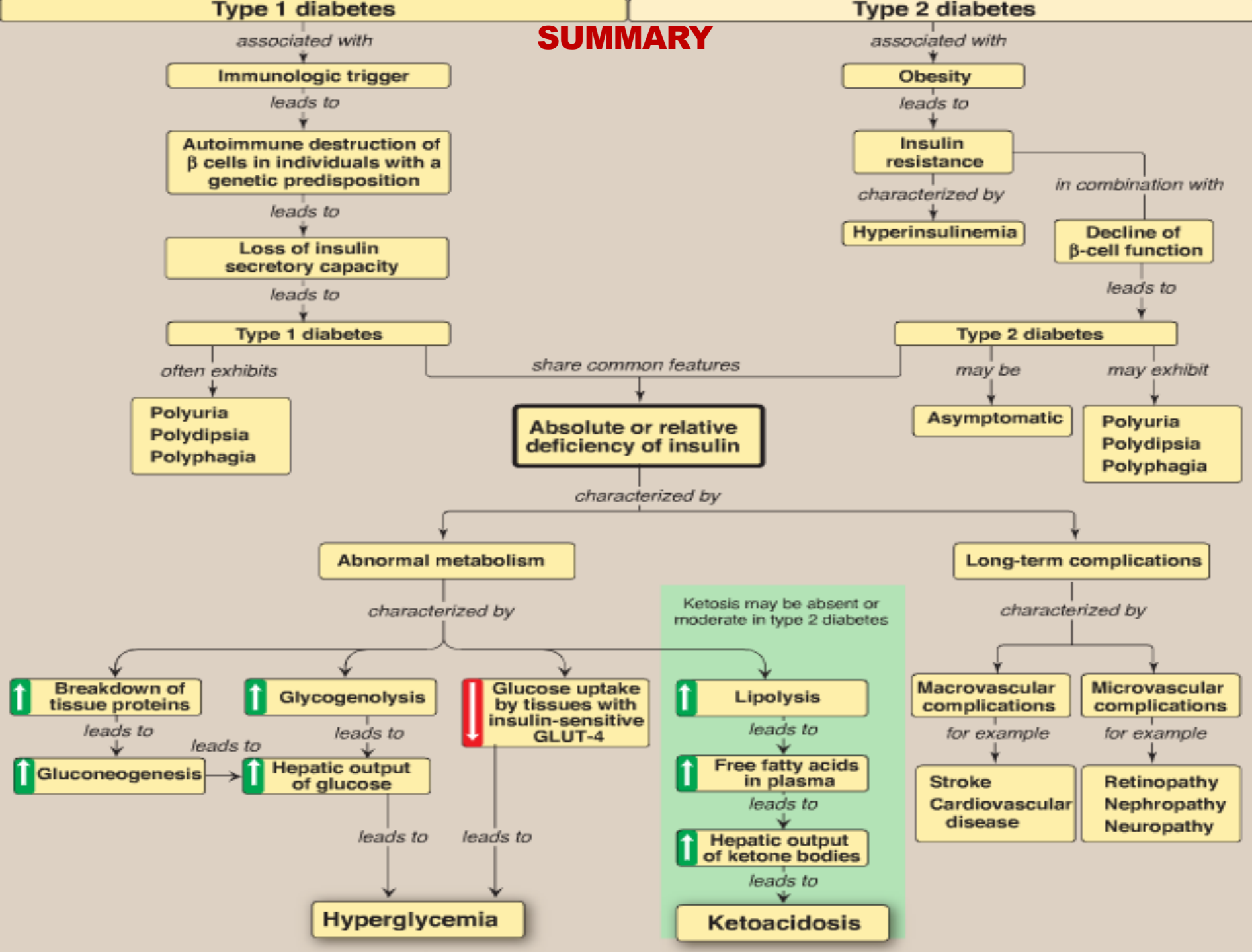


Most of the tissues lack sorbitol dehydrogenase (normally), but there are no manifestations of sorbitol because the blood glucose is under the control.

Glucose → sorbitol
(by **aldose reductase**)

Sorbitol → fructose
(by **sorbitol dehydrogenase**)




Type 1 diabetes
Type 2 diabetes
SUMMARY
associated with
Immunologic trigger
leads to
Autoimmune destruction of β cells in individuals with a genetic predisposition
leads to
Loss of insulin secretory capacity
leads to
Type 1 diabetes
often exhibits
Polyuria
Polydipsia
Polyphagia
associated with
Obesity
leads to
Insulin resistance
characterized by
Hyperinsulinemia
in combination with
Decline of β-cell function
leads to
Type 2 diabetes
may be
Asymptomatic
may exhibit
Polyuria
Polydipsia
Polyphagia
share common features
Absolute or relative deficiency of insulin
characterized by
Abnormal metabolism
characterized by
Breakdown of tissue proteins
leads to
Gluconeogenesis
Glycogenolysis
leads to
Hepatic output of glucose
leads to
Glucose uptake by tissues with insulin-sensitive GLUT-4
leads to
Hyperglycemia
Ketosis may be absent or moderate in type 2 diabetes
Lipolysis
leads to
Free fatty acids in plasma
leads to
Hepatic output of ketone bodies
leads to
Ketoacidosis
Long-term complications
characterized by
Macrovascular complications
for example
Stroke
Cardiovascular disease
Microvascular complications
for example
Retinopathy
Nephropathy
Neuropathy

MCQs

Q1 - Glucose is metabolized to sorbitol within the cells by which enzyme ?

A- sorbitol dehydrogenase

B- aldose reductase

C- HMG CoA synthase

Q2 -which of the following is A major cause of morbidity in DM ?

A- blindness

B- end-stage renal disease

C- infections

Q3 – in the beginning of Diabetic Nephropathy the GFR will be ?

A- increased

B- debased

C- normal

Q4 – which of the following is The earliest clinical finding of diabetic nephropathy ?

A- proteinuria

B- microalbuminuria

C- end-stage renal disease

D-Glycosuria

Q5-Which one of the following is a metabolic effect of insulin:

A) increase Lipolysis

B) Decrease Fatty acid oxidation

C) increasea Glycogenolysis

Q6- A diabetic patient came to the hospital for a follow up appointment, the doctor told him that his glucose level is under control but the doctor was worried because the patient has developed some mild complications, which of the following tests It is used to estimate glycemic control in the last 1-2 months ?

A- FPG

B- OGTT

C- A1C

Q7 – A 20 years old male was fasting for 12 hours came to the hospital for full medical check up , after that the doctor told him the blood glucose level is 115mg/dl what is your Interpretation ?

A- he Has diabetes

B- he has risk to devolve DM

C- he is normal

Answer key:1.B 2.A 3.A 4.B 5.B 6.C 7.B

SAQs

Q1 Mention 3 General Mechanisms for Diabetic Microvascular Complications ?

1. AGEs of essential cellular proteins → cellular defects
2. ↑Intracellular sorbitol → ↑ cell osmolality → cellular swelling
3. ↑ ROS → oxidative stress → cell damage

Q2- sorbitol is converted to fructose by which enzymes?

aldose reductase then sorbitol dehydrogenase

Q3 What is the Mechanisms of Decrease of Peripheral Glucose Uptake in muscle ?

Decrease insulin

↓

decrease Glucose & amino acid uptake and increase protein break down

↓

increase Plasma glucose and Plasma amino acids

Biochemistry Bandits 434

اللهم إني استودعتك ما قرأت وما حفظت وما تعلمت فرده لي عند حاجتي إليه إنك على كل شيء قدير

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