وَقُل رَّبِّ زِدْنِي عِلْمًا

النادي الطبي

PERIPHERAL NERVOUS SYSTEM

SUBJECT : Biochemistry

LEC NO. : 2

DONE BY : Batool ALzubaidi

#كلينيكال_إلا_شحطة

Biochemistry of peripheral nerves

Ahmed Salem, MD, PhD, FRCR

Topics

- Diabetes Mellitus (DM)

- Peripheral neuropathy due to vitamin deficiency/ uremic syndrome

السلايد الي محطوط عندها FYI يعني لمعلوماتك مش للامتحان بس انا راح احط هايلايت و اكتب اذا في زيادة عشان اطلع من خطيتكم

كل المحاضرة لمعلوماتكم ما عدا ٤ سلايدات راح احط عندهم نجوم بالازرق

FYI

Diabetes Mellitus (DM)

حكى الحكي عن ال diabet هو فقط مراجعة مش مطلوب منك بالامتحان الهايلايات الي قراه للاحتياط

- Syndrome of disordered metabolism leading to high blood sugar levels
  - Due to combination of environmental and heredity factors
  - Defect in insulin secretion or action

- Blood sugar levels are controlled by complex interaction of multiple chemicals & hormones (especially insulin made in beta cells of pancreas)

- Signs and symptoms
  - Hyperglycaemia
  - Glycosuria
  - Polyuria
  - Polydipsia
  - Polyphagia

TEST CRITERIA	PREDIABETES	OVERT DIABETES MELLITUS
HbA1c	5.7% to 6.4%	≥ 6.5%
Fasting plasma glucose test (mg/dL)	100 to 125	≥ 126
Plasma glucose after 75 g oral glucose tolerance test	140 to 199	2 hours: ≥ 200
Random plasma glucose test with symptoms of hyperglycemia (mg/dL)	Not applicable	≥ 200

FYI

Type 1: Insulin dependent DM (10%)

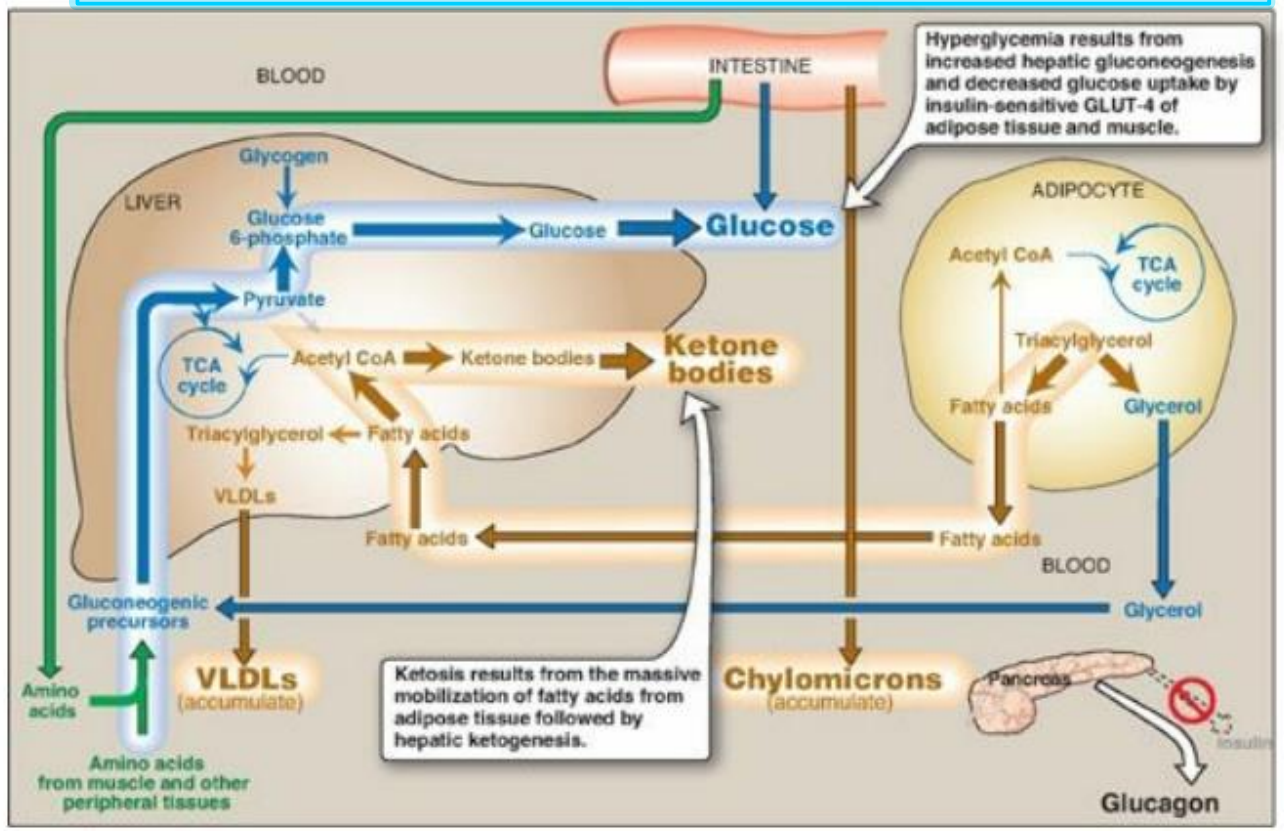
- **Cause:** autoimmune destruction of beta cells of pancreas → insulin is absent/ deficient

- **Metabolic changes**
  - CHO metabolism
  - Fat metabolism
  - Protein metabolism

- **Symptoms:** fatigue, weight loss, weakness

- **Treatment:** insulin

راح يكون في كتير جلوكوز بالدم جسمك راح يشغل gluconeogenesis و وقتها
راح تكون تستهلك amino acids and proteins و راح يصير معك muscle
wasting و ثانيا راح تكون تستهلك oxaloacetate و وقتها ال Krebs cycle ما
راح تكون تشتغل منيح و راح يتفاقم وجود ال acetyl coA و النتيجة ketosis

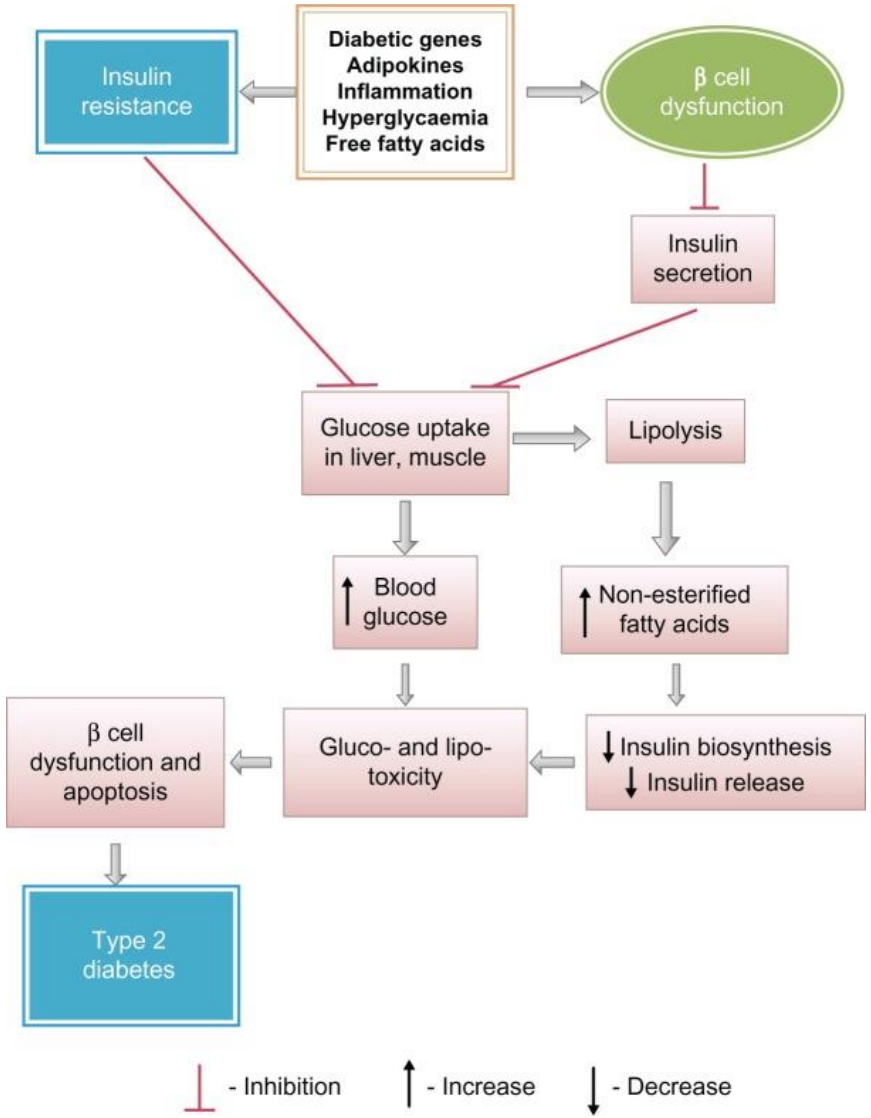


FYI

hyperosmolar nonketotic hyperglycemia هدول معرضين يصيرلهم

Type 2: Insulin independent DM (90%)

- **Cause:** combination of insulin resistance & dysfunctional beta cells
  - Insulin is present in normal to elevated levels
  - Down regulation of insulin receptors
- **Metabolic changes**
  - CHO metabolism (correlated to diet)
  - Fat metabolism
  - Protein metabolism
- **Symptoms:** DM develops gradually with no symptoms at first, most pts are obese
- **Treatment:** diet, weight loss, exercise, oral hypoglycaemic agents, pts might need insulin in end



FYI

Diabetes: Complications

Acute

- Diabetic Ketoacidosis(DKA)
- Hyperosmolar hyperglycemic state (HHS)

Chronic

Microvascular

- Diabetic Retinopathy
- Diabetic Nephropathy (Diabetic Kidney disease)
- Diabetic Neuropathy

Macrovascular

- Coronary heart disease,
- Cerebrovascular disease
- Peripheral vascular disease

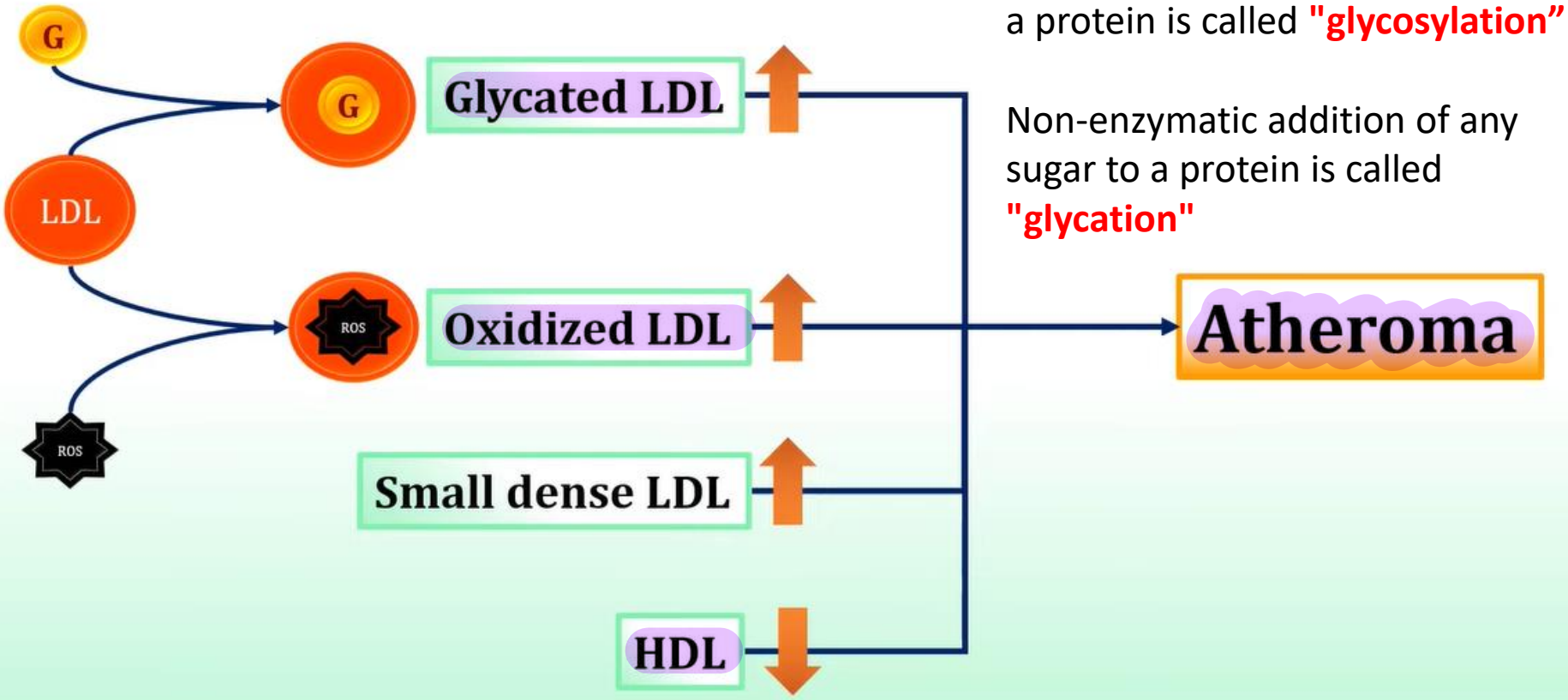
Others

- Cataract, Glaucoma
- Infections, Foot ulcers
- Skin infections
- fungal infections

FYI

Diabetes and Atherosclerosis: Macrovascular Complications

HYPERGLYCEMIA

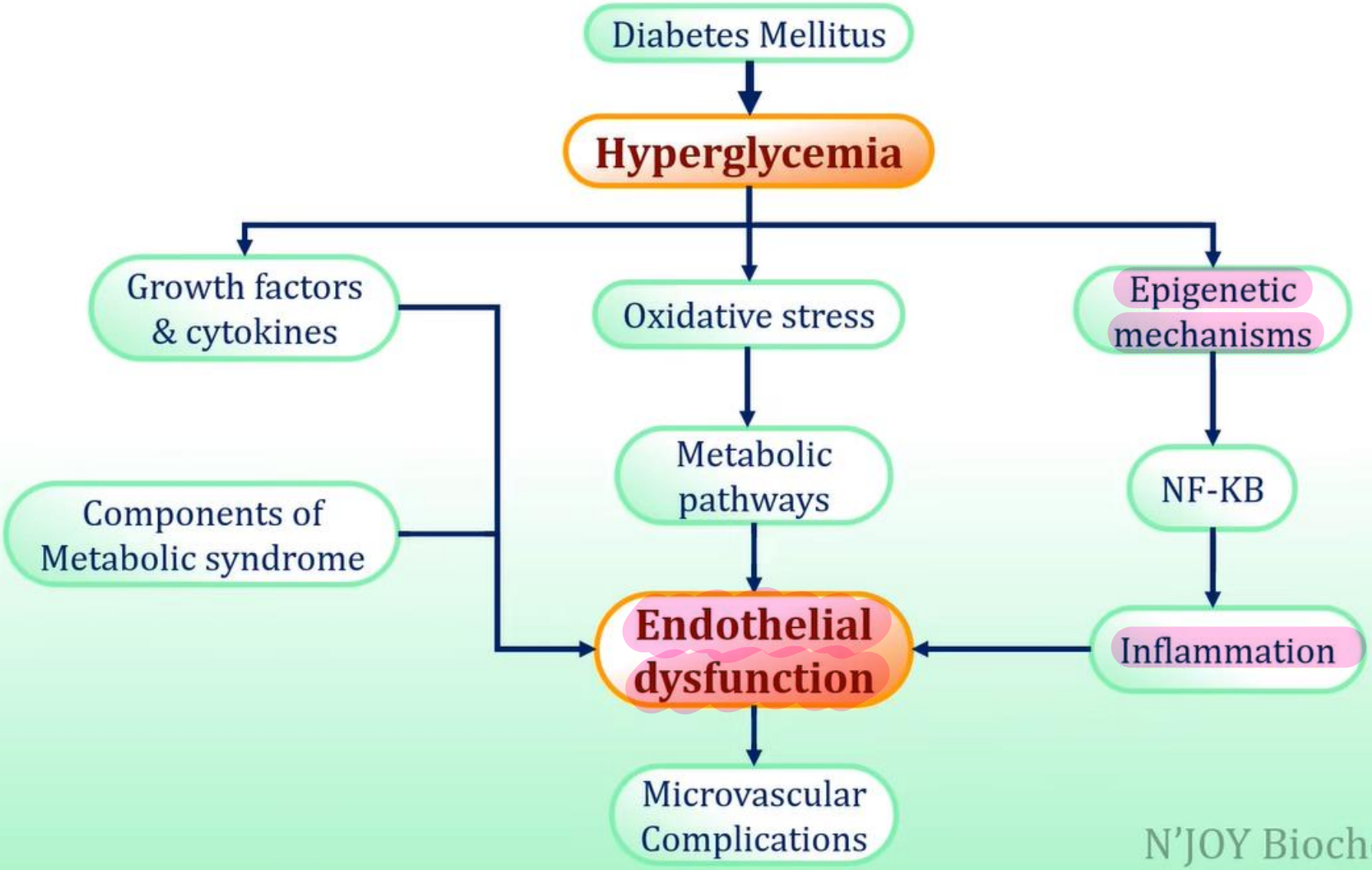


Enzymatic addition of any sugar to a protein is called **"glycosylation"**

Non-enzymatic addition of any sugar to a protein is called **"glycation"**

FYI

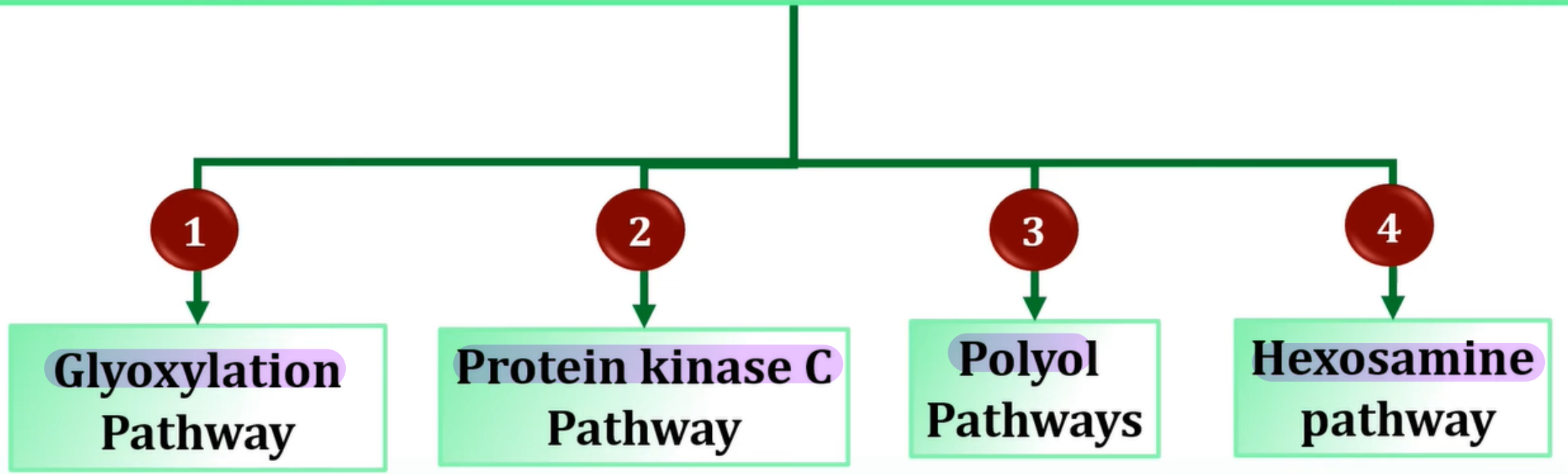
Molecular Mechanisms of Macro/Microvascular complications



N'JOY Biochemistry

FYI

Hyperglycemia: Activation of Metabolic Pathways



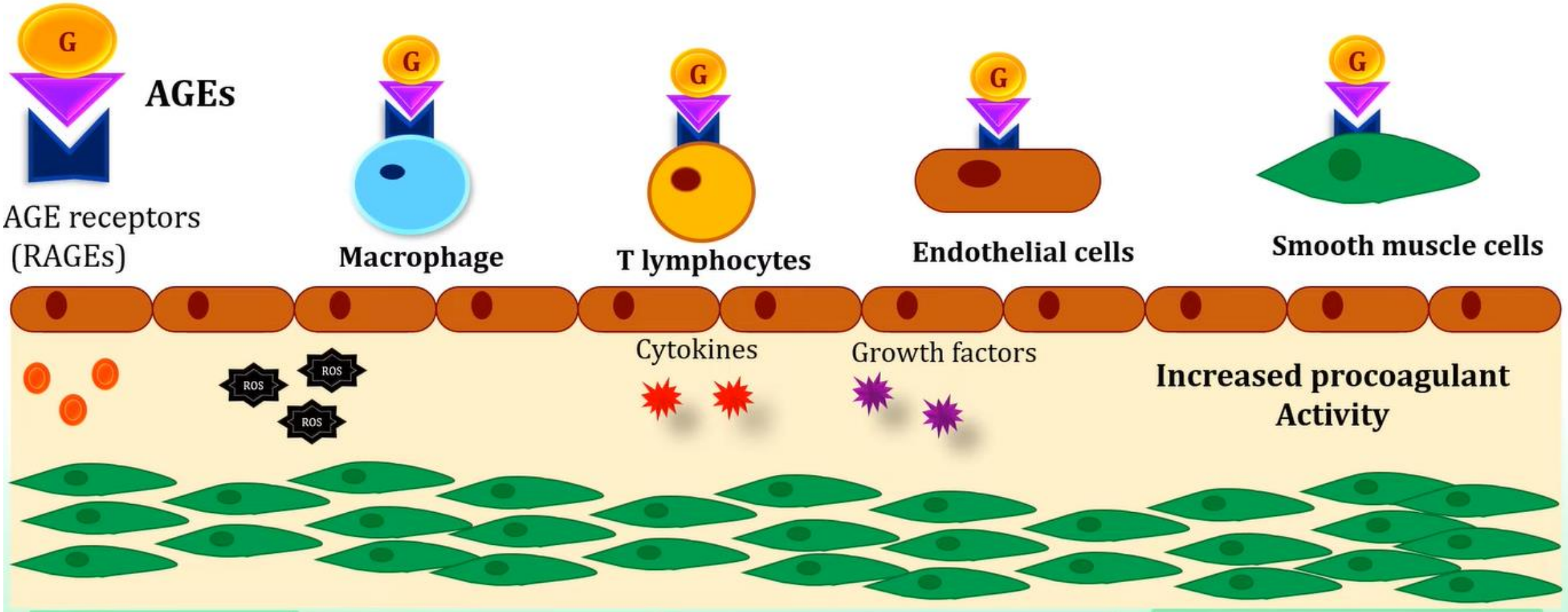
Advanced Glycation end products (AGEs)

Modification of

- Intracellular protein
- Extracellular matrix protein and components
- Plasma protein

FYI

1: Glyoxylation pathway: Advanced Glycation End Products (AGEs)



Trapping of LDL

Generation of reactive Oxygen species (ROS)

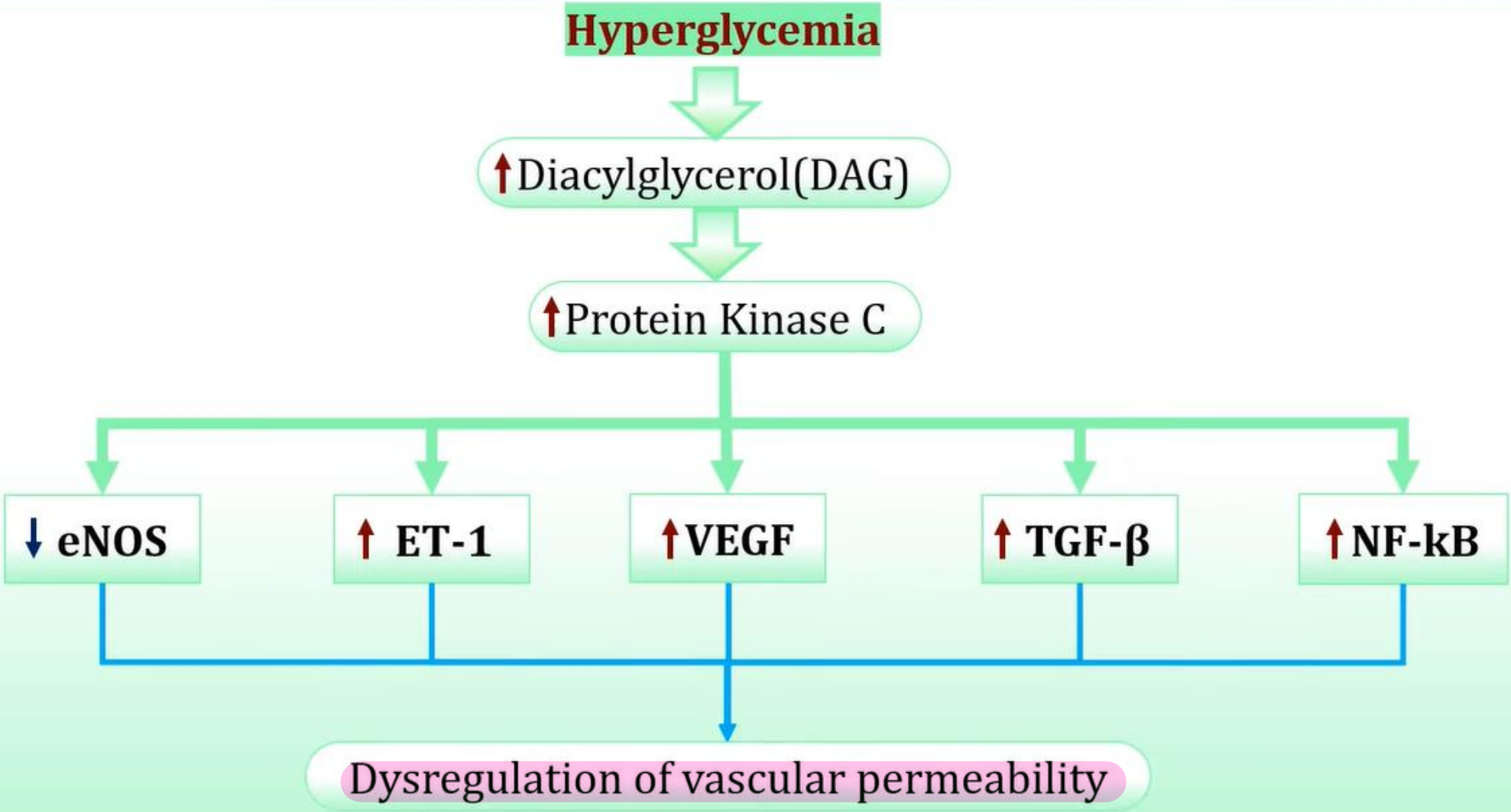
Release of cytokines, growth factors (TGFβ),VEGF

Proliferation of Vascular smooth muscle cells & Synthesis of ECM

Effects of glycation

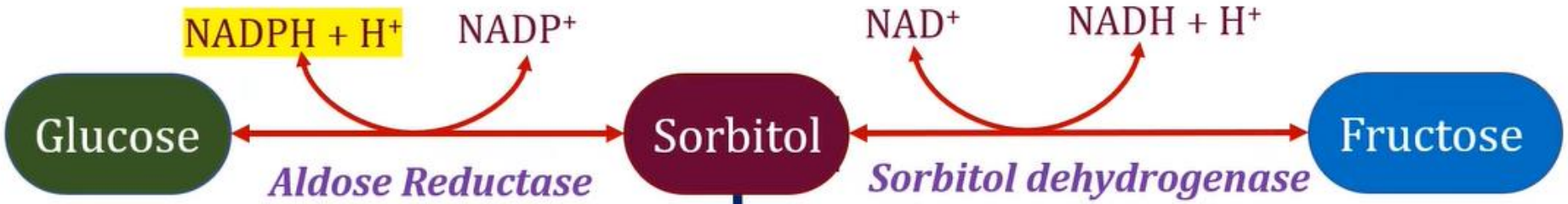
FYI

2: Activation of Protein kinase C



3: Polyol pathways

- Polyol pathway: Sorbitol is a polyhydric sugar alcohol



High Km
For glucose

Activation of pathway in DM

- Eye lens,
- Kidneys,
- Nervous tissues

(Schwann cells of the nerve sheath)

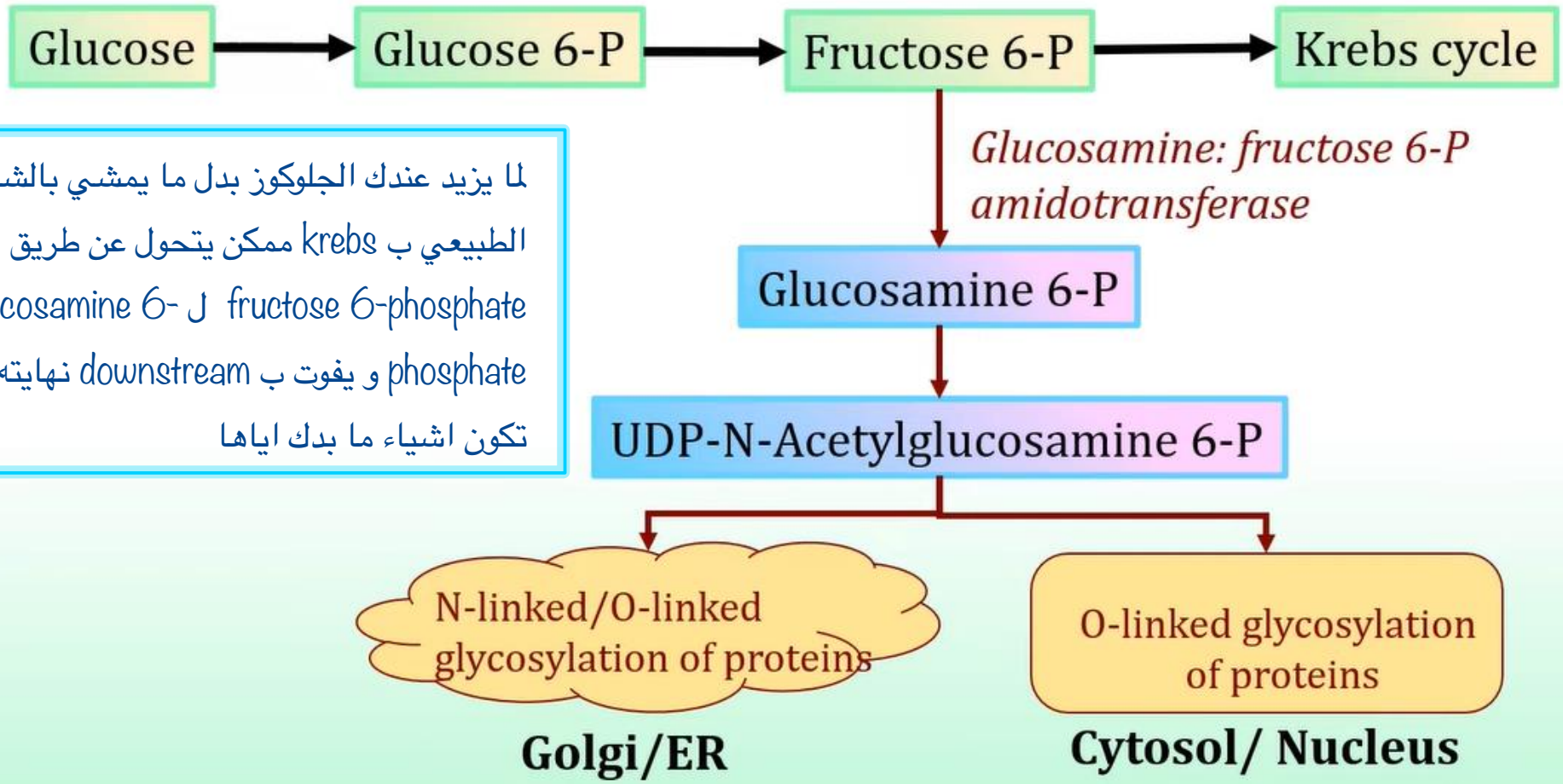
- Liver
- Seminal vesicles
- (Fructose-Fuel of spermatozoa)

- Cataract
- Nephropathy
- Neuropathy

ال sorbitol هو ال alcohol of glucose مفيد للتحويل من glucose ل fructose خصوصا بال seminal vesicles و لكن المشكلة بس يزيد كتير و ما تقدر تتخلص منه بصير عرضة انك يعمل مضاعفات السكري

FYI

4: Hexosamine Pathway



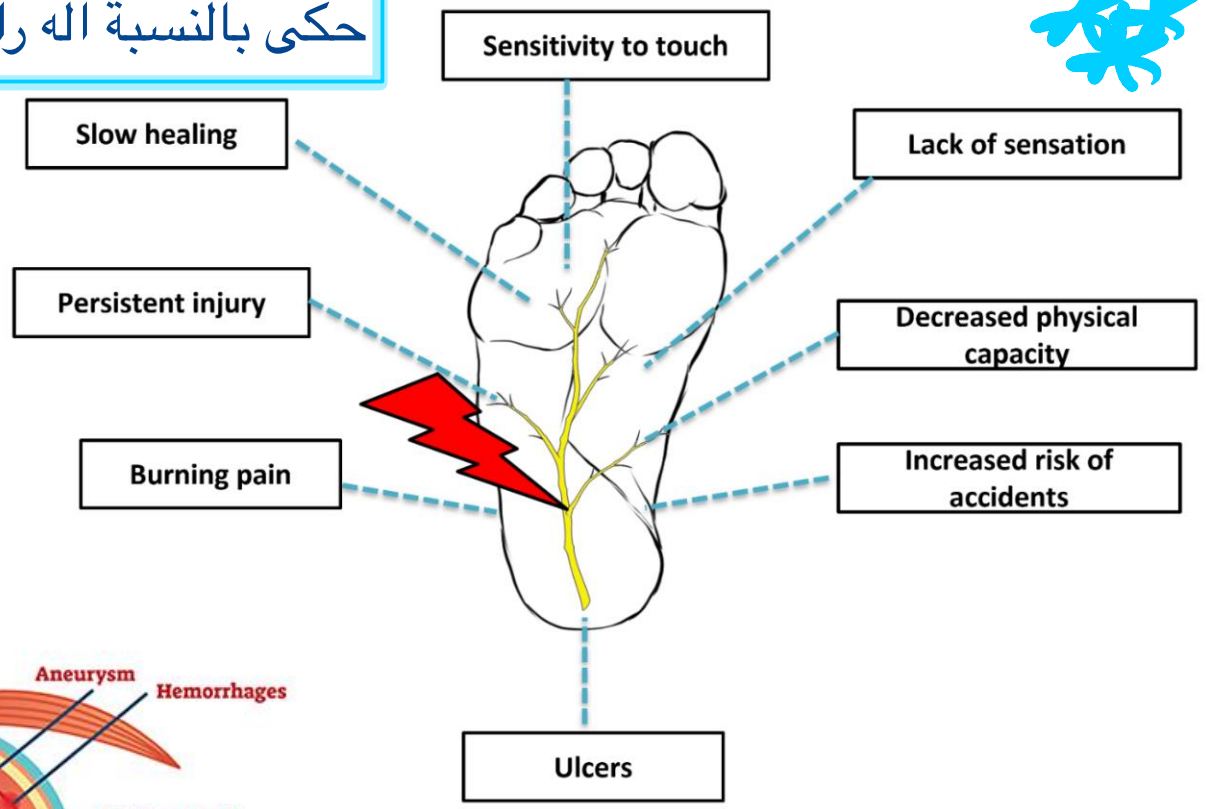
لما يزيد عندك الجلوكوز بدل ما يمشي بالشكل الطبيعي ب krebs ممكن يتحول عن طريق ال fructose 6-phosphate ل glucosamine 6- و يفوت ب phosphate نهايته downstream تكون اشياء ما بدك اياها

- Increased expression of TGF-β
- Modification of eNOS(Nitric oxide synthase)

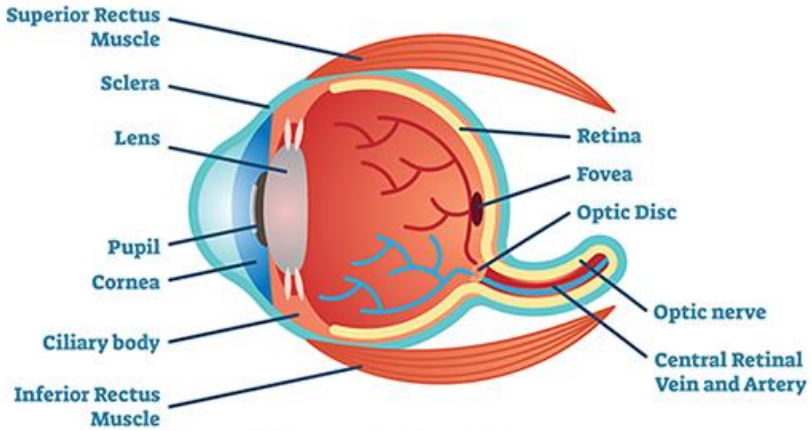
hemistry

كتير مهم و راح يجي بالامتحان

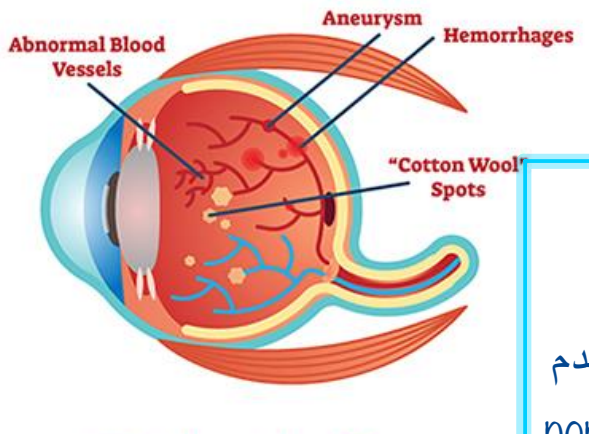
حكى بالنسبة اله راح يحطلنا اسئلة سهلة 🤍



ليش بصير new vessels formation بسبب ال hypoxia ال blood vessels الي بتغذي ال retina ماكلة هوا ال permeability سيئة فيها hemorrhages فبصير activation انه يتكون vessels جديدة .. اشي مهم انه بسبب ال vessels الجديدة ممكن يتسكر ال drainage تا ع ال eye و يصير glaucoma



Healthy Eye



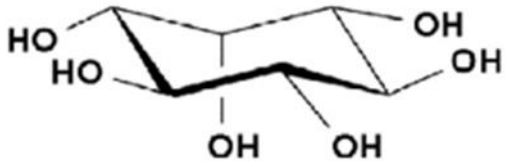
Diabetic Eye

من الفروقات بين ال healthy and diabetic eye اولا ال cataract ثانيا diabetic retinopathy و منها نوعين (جدا مهم جاي بالامتحان) النوع الاول proliferative هو بكون متقدم و فيه new vessels formation النوع التاني الي قبل هاد non proliferative بصير vascular endothelial dysfunction و بصير micro aneurysm و hemorrhages و cotton wool spots و هدول سببهم اختلال ال vascular permeability

لو جابلنا صورتين ل retina اتطلع على عدد ال vessels و عدهم قد بعض او لا عشان تحكم هو proliferative او لا

Peripheral neuropathy due to vitamin deficiency/ uremic syndrome

- **Uremic syndrome:** terminal manifestation of renal failure
  - Myoinositol is the basis for peripheral neuropathy



myo-inositol

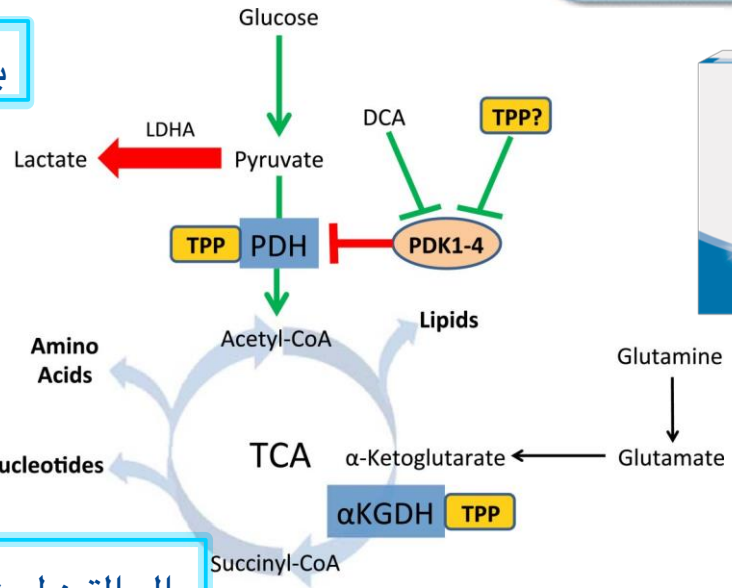
CENTRAL NERVOUS SYSTEM

MI is essential for the development and function of peripheral nerves (Chau et al, 2005)

- **Vitamins:**
  - **Thiamine (B1)** → reduced ATP → impaired cellular function
  - **B6 (pyridoxal phosphate)** → reduced formation of phospholipids (isoniazid interferes with B6 absorption)
    - Toxicity causes sensory neuropathy!
  - **B12** → demyelination of nerves

pyruvate dehydrogenase enzyme ل cofactor بكون

Co-factor for a keto glutarate dehydrogenase



بالحالتين لو زاد او قل vitamin b6 راح يعمل peripheral neuropathy ليش ؟ لانه موجود ب شكلين واحد active و التاني preactive فلو زاد ال preactive راح يعمل inhibition لل active