Biochemistry of peripheral nerves

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Topics

- Diabetes Mellitus (DM)

- Peripheral neuropathy due to vitamin deficiency/ uremic syndrome

Diabetes Mellitus (DM)

- 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

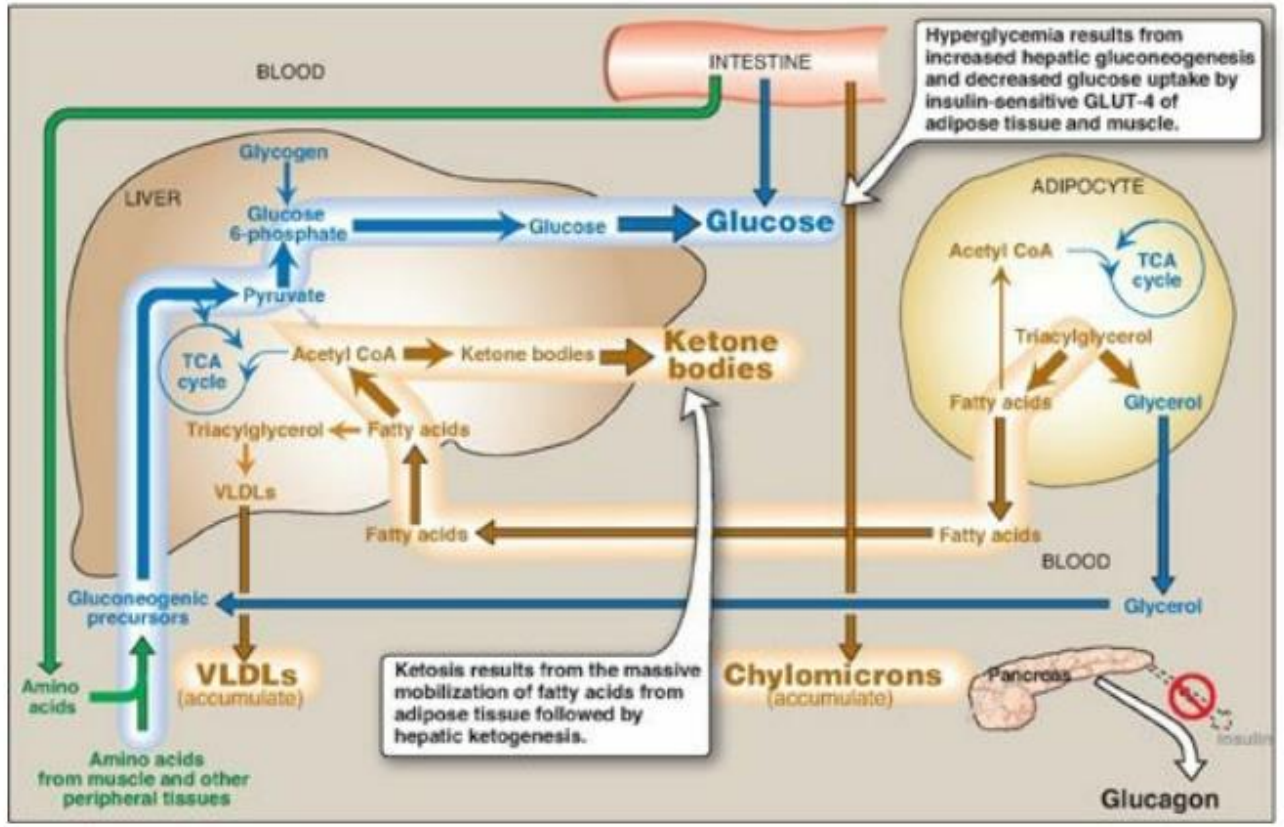
Type 1: Insulin dependent DM (10%)

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

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

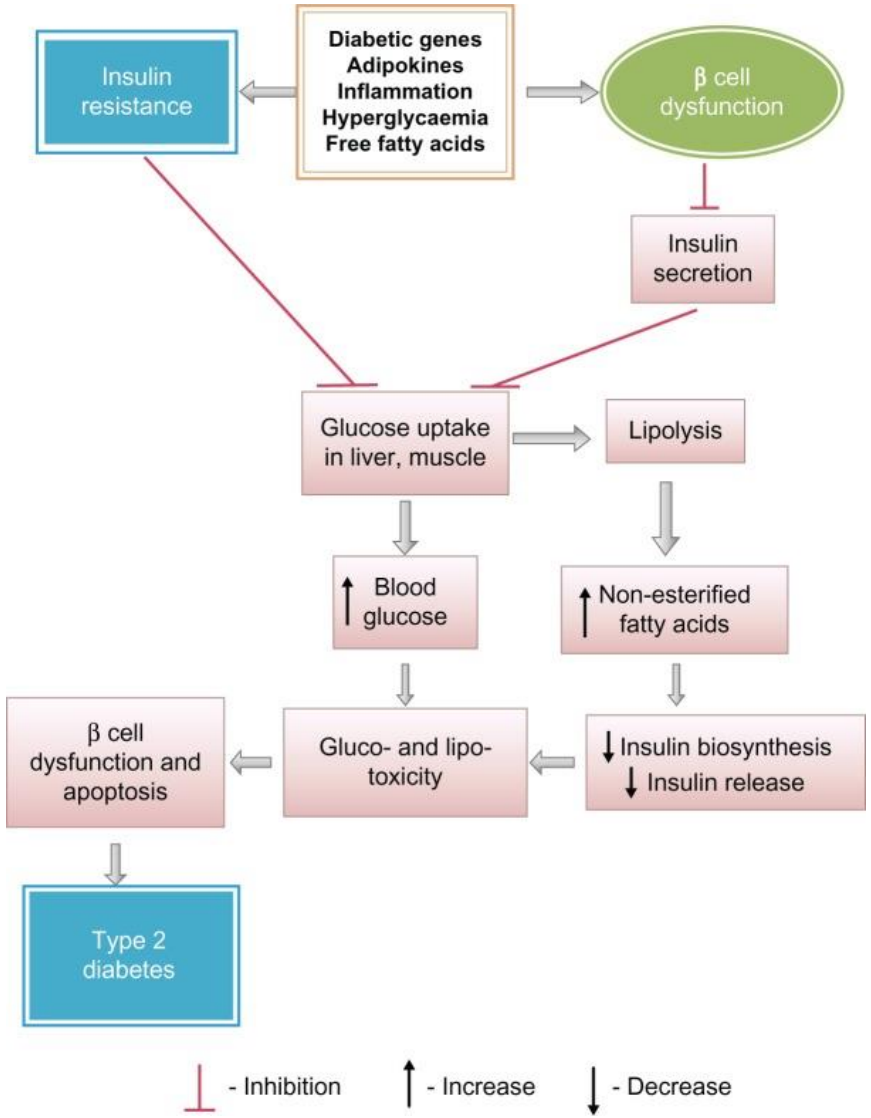
- **Symptoms:** fatigue, weight loss, weakness

- **Treatment:** insulin



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



Diabetes: Complications

Acute

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

Chronic

Macrovascular

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

Microvascular

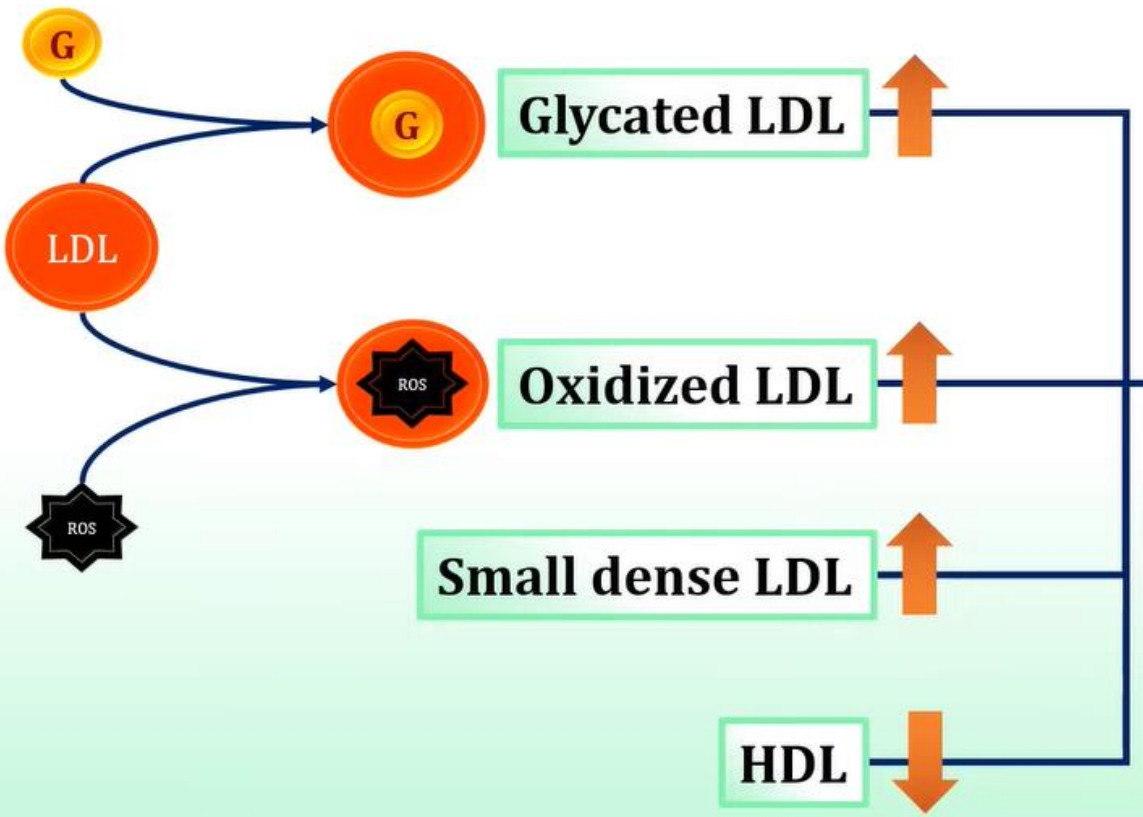
- Diabetic Retinopathy
- Diabetic Nephropathy (Diabetic Kidney disease)
- Diabetic Neuropathy

Others

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

Diabetes and Atherosclerosis: Macrovascular Complications

HYPERGLYCEMIA

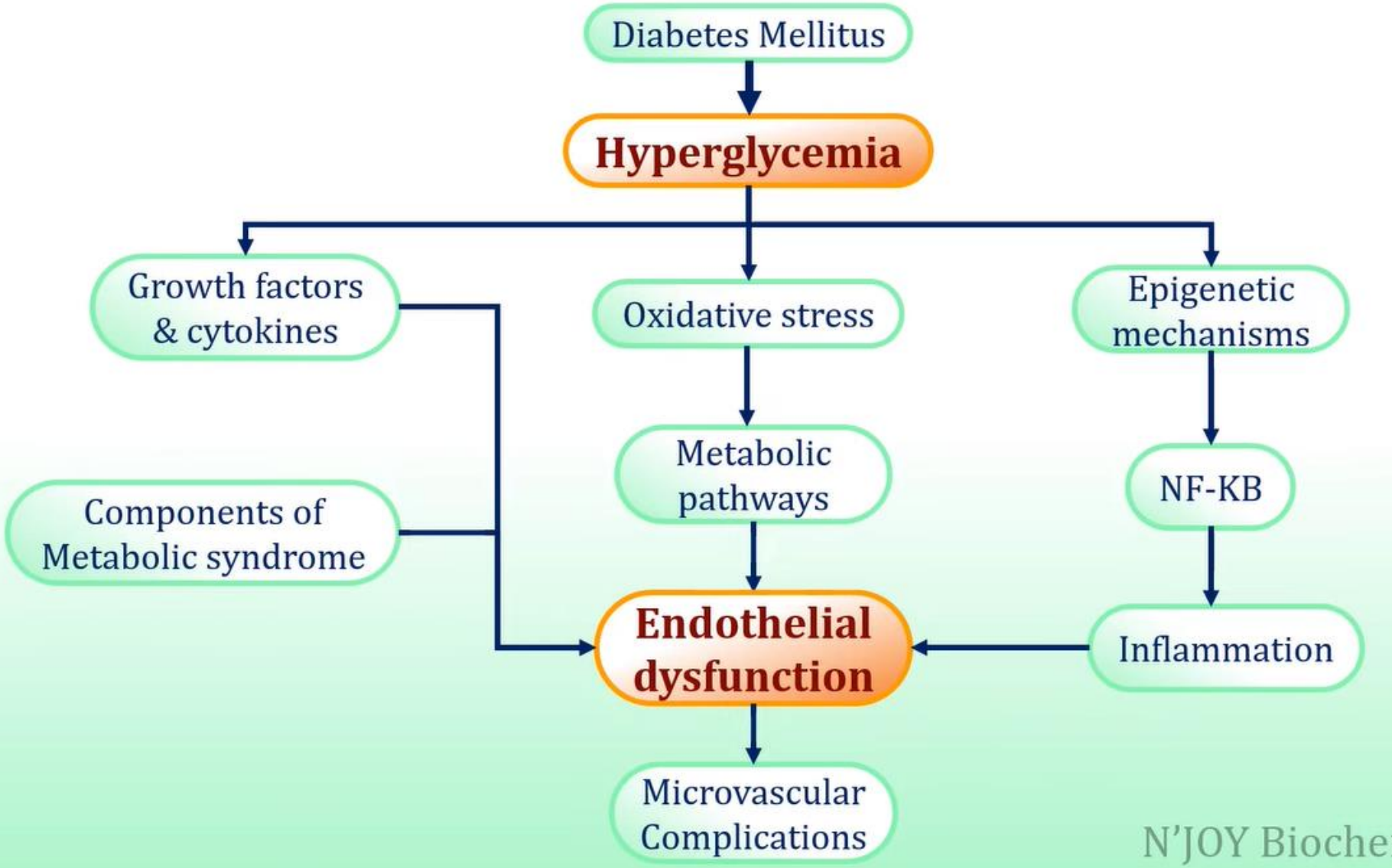


Enzymatic addition of any sugar to a protein is called **"glycosylation"**

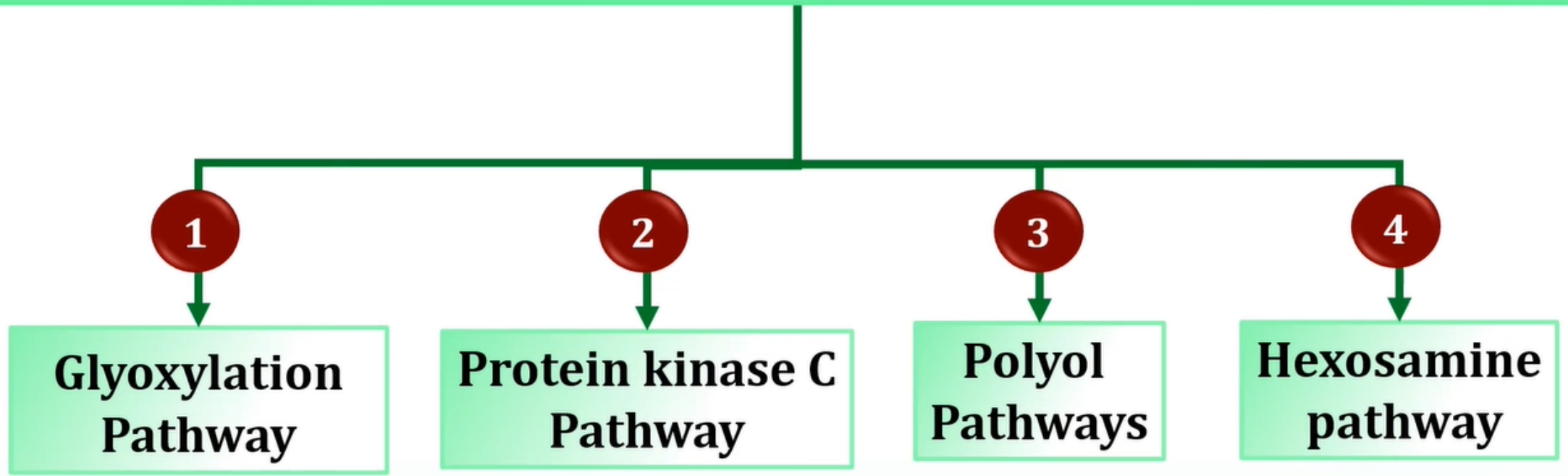
Non-enzymatic addition of any sugar to a protein is called **"glycation"**

Atheroma

Molecular Mechanisms of Macro/Microvascular complications



Hyperglycemia: Activation of Metabolic Pathways

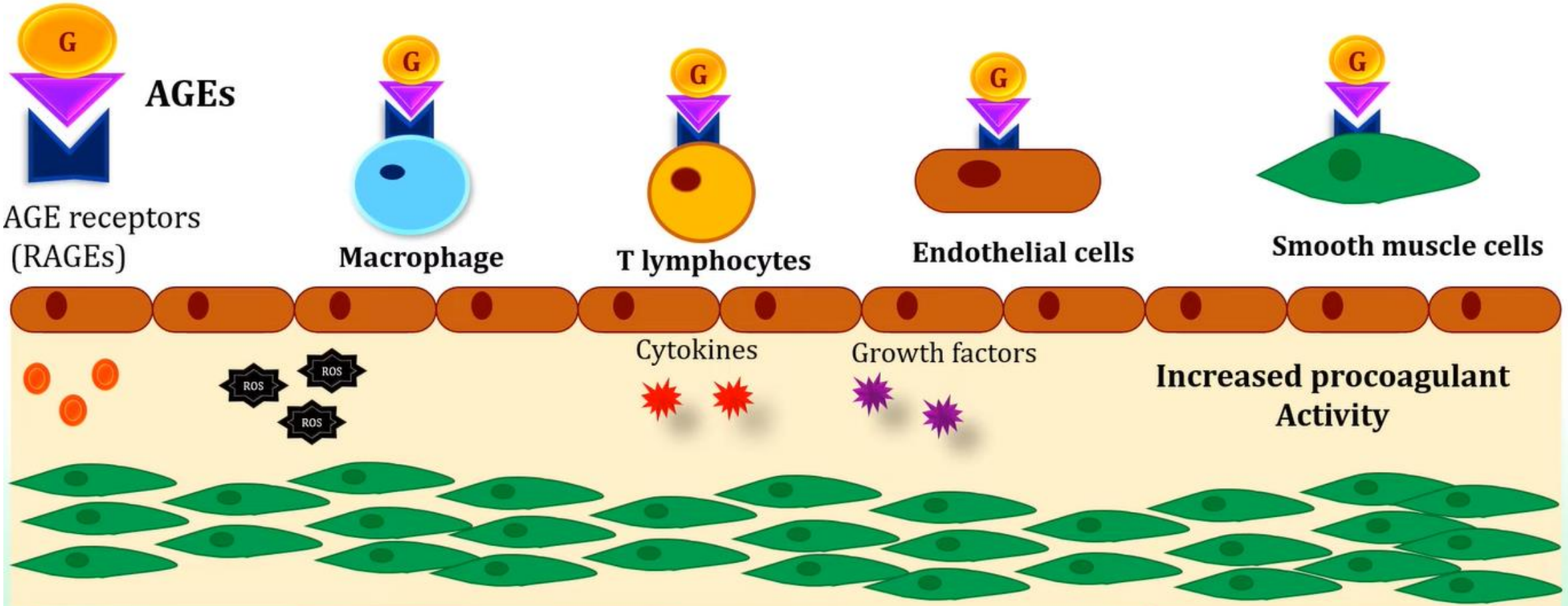


Advanced Glycation end products (AGEs)

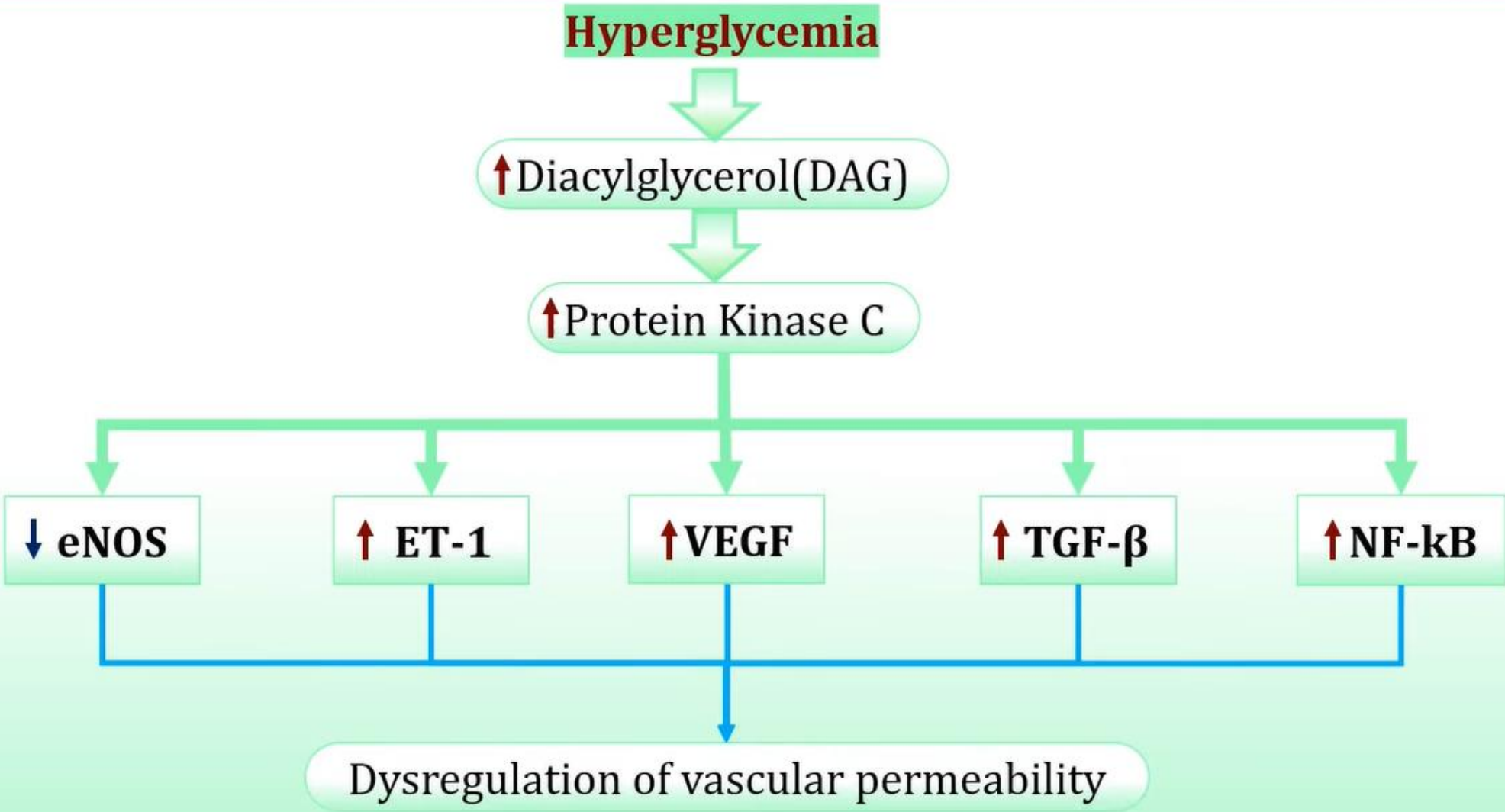
Modification of

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

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



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

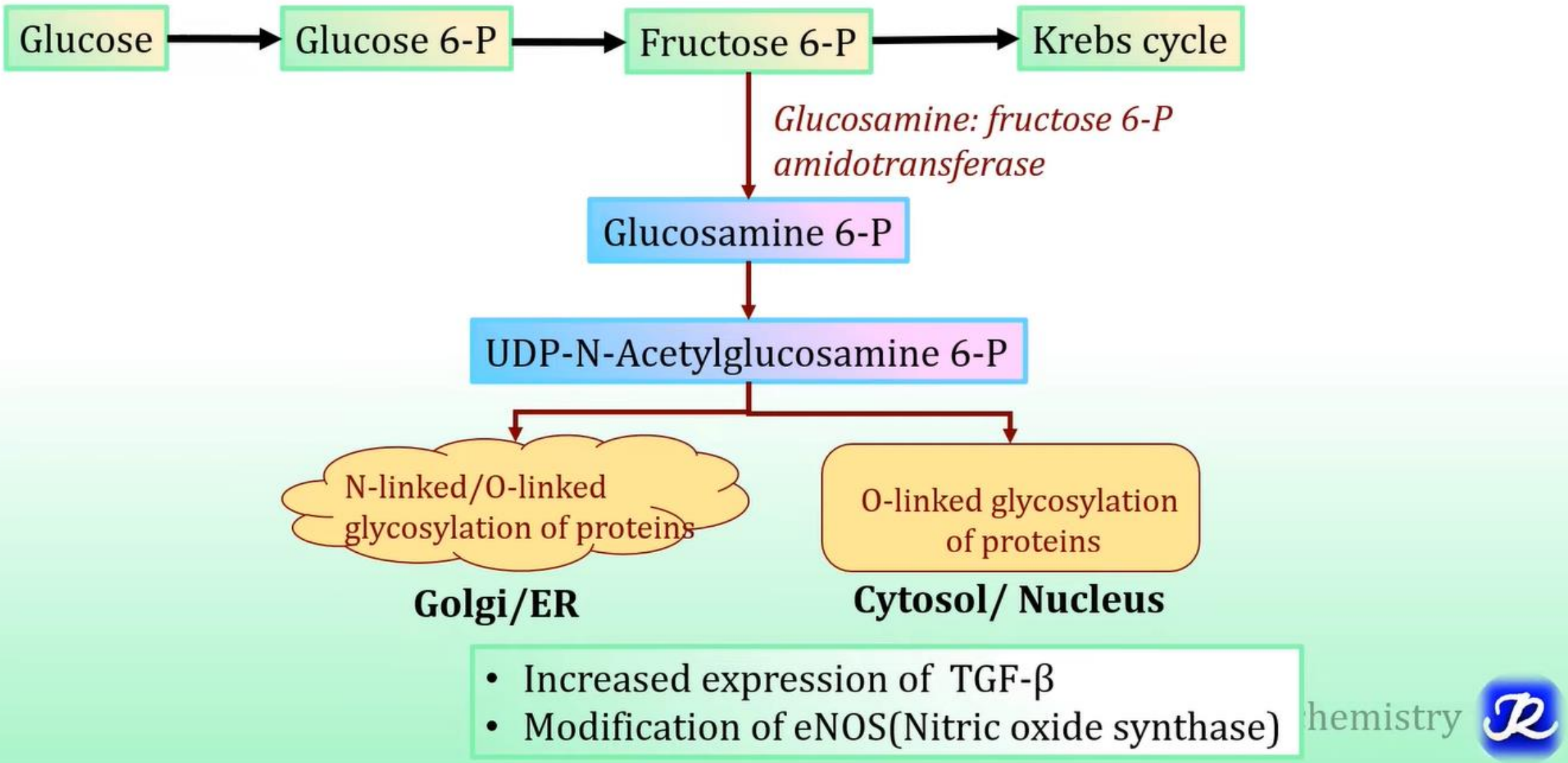
- Eye lens,
- Kidneys,
- Nervous tissues

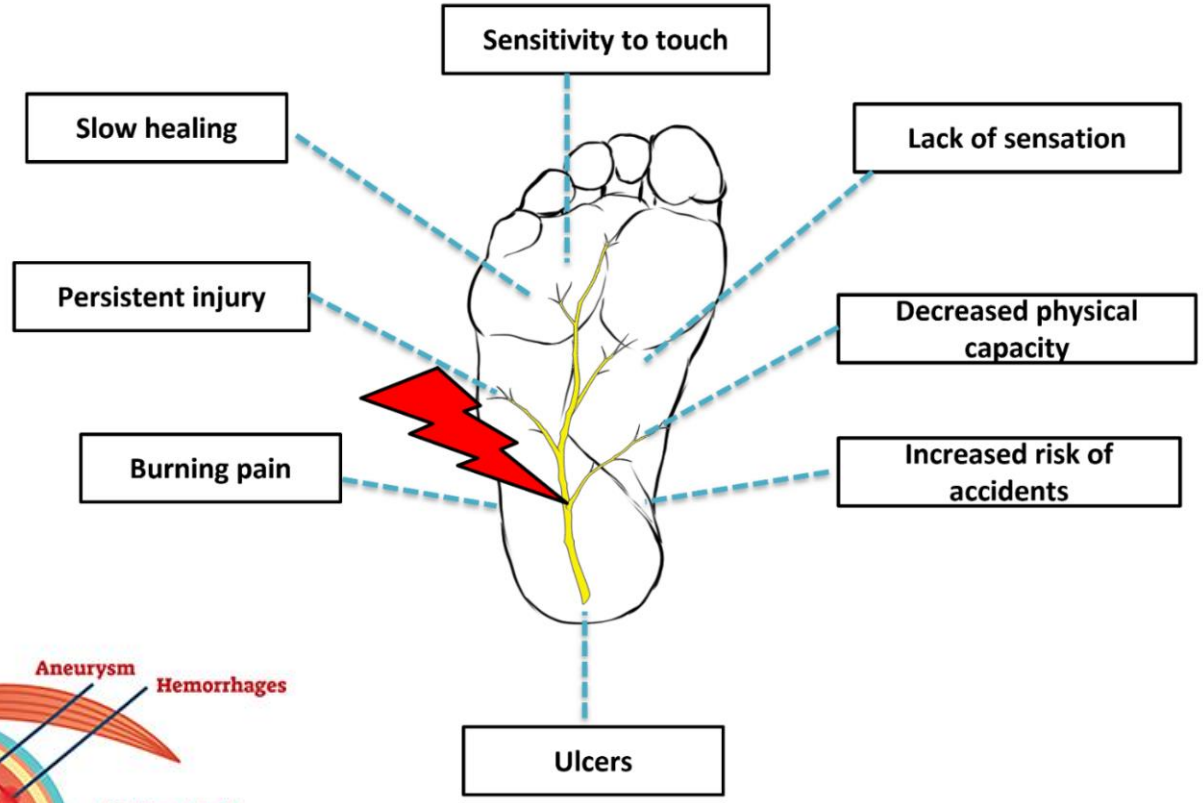
(Schwann cells of the nerve sheath)

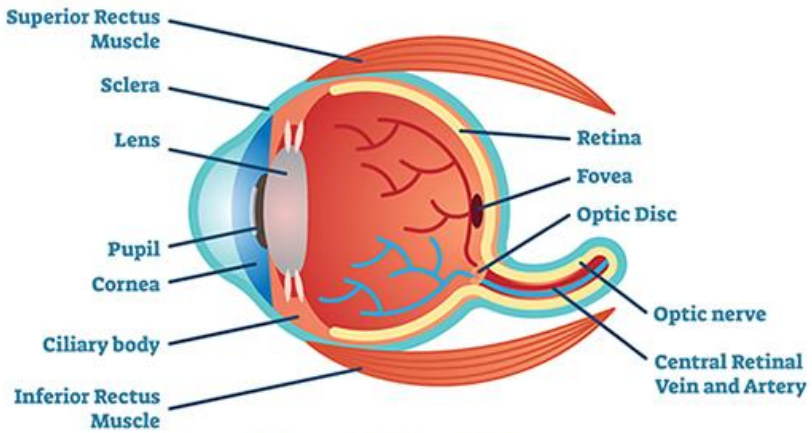
- Liver
- Seminal vesicles
- (Fructose-Fuel of spermatozoa)

- Cataract
- Nephropathy
- Neuropathy

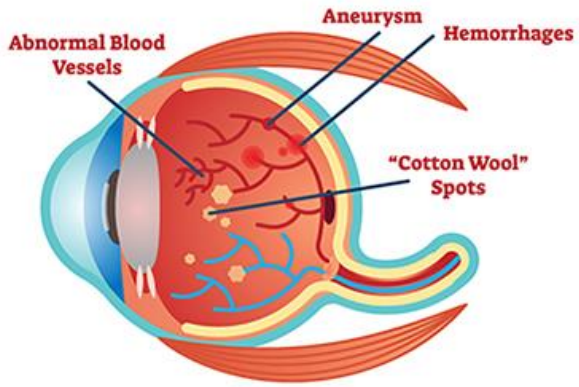
4: Hexosamine Pathway







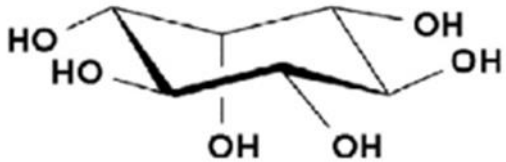
Healthy Eye



Diabetic Eye

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