Diabetes Mellitus

WHO

- Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced.
- results in increased concentrations of glucose in the blood, which in turn damage the blood vessels and nerves.

- Diabetes mellitus is a group of metabolic disorders sharing the common feature of hyperglycemia

Classification

- two principle forms of diabetes:
  1. Type 1 diabetes (formerly known as insulin-dependent)
  2. Type 2 diabetes (formerly named non-insulin-dependent)

Table 24-6 Classification of Diabetes Mellitus

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated Idiopathic
Type 2 diabetes (combination of insulin resistance and β-cell dysfunction)
Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY), caused by mutations in: Hepatocyte nuclear factor 4α (*HNF4A*), MODY1 Glucokinase (*GCK*), MODY2 Hepatocyte nuclear factor 1α (*HNF1A*), MODY3 Pancreatic and duodenal homeobox 1 (*PDX1*), MODY4 Hepatocyte nuclear factor 1β (*HNF1B*), MODY5 Neurogenic differentiation factor 1 (*NEUROD1*), MODY6 Neonatal diabetes (activating mutations in *KCNJ11* and *ABCC8*, encoding Kir6.2 and SUR1, respectively) Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (m.3243A→G) Defects in proinsulin conversion Insulin gene mutations
Genetic defects in insulin action
Type A insulin resistance Lipoatrophic diabetes
Exocrine pancreatic defects
Chronic pancreatitis Pancreatectomy/trauma Neoplasia Cystic fibrosis Hemochromatosis Fibrocalculous pancreatopathy
Endocrinopathies
Acromegaly Cushing syndrome Hyperthyroidism Pheochromocytoma Glucagonoma
Infections
Cytomegalovirus Coxsackie B virus Congenital rubella
Drugs
Glucocorticoids Thyroid hormone Interferon-α Protease inhibitors β-adrenergic agonists Thiazides Nicotinic acid Phenytoin (Dilantin) Vacor
Genetic syndromes associated with diabetes
Down syndrome Klinefelter syndrome Turner syndrome Prader-Willi syndrome
Gestational diabetes mellitus

ETIO-PATHOGENESIS

- PATHOGENESIS OF TYPE 1 DM. destruction of β-cell mass, usually leading to absolute insulin deficiency.

1. Genetic susceptibility- HLA gene cluster on chromosome 6p21, which according to some estimates contributes as much as 50% of the genetic susceptibility to type 1 diabetes.

- Allele-HLA-DR3-DR4

2.Autoimmune factors: fundamental immune abnormality in type 1 diabetes is a **failure of self-tolerance** in T cells specific for islet antigens

- islet cell antibodies
- insulitis
- Selective destruction of β-cells

- TH1 cells secrete-IFN-γ and TNF
- Islet autoantigens-β cell enzyme glutamic acid decarboxylase (GAD), and islet cell autoantigen 512(ICA512)
- **cell-mediated autoimmunity**
- Associated with other autoimmune diseases

3.Environmental factors

- viral infections
- Chemicals-alloxan, streptozotocin and pentamidine.

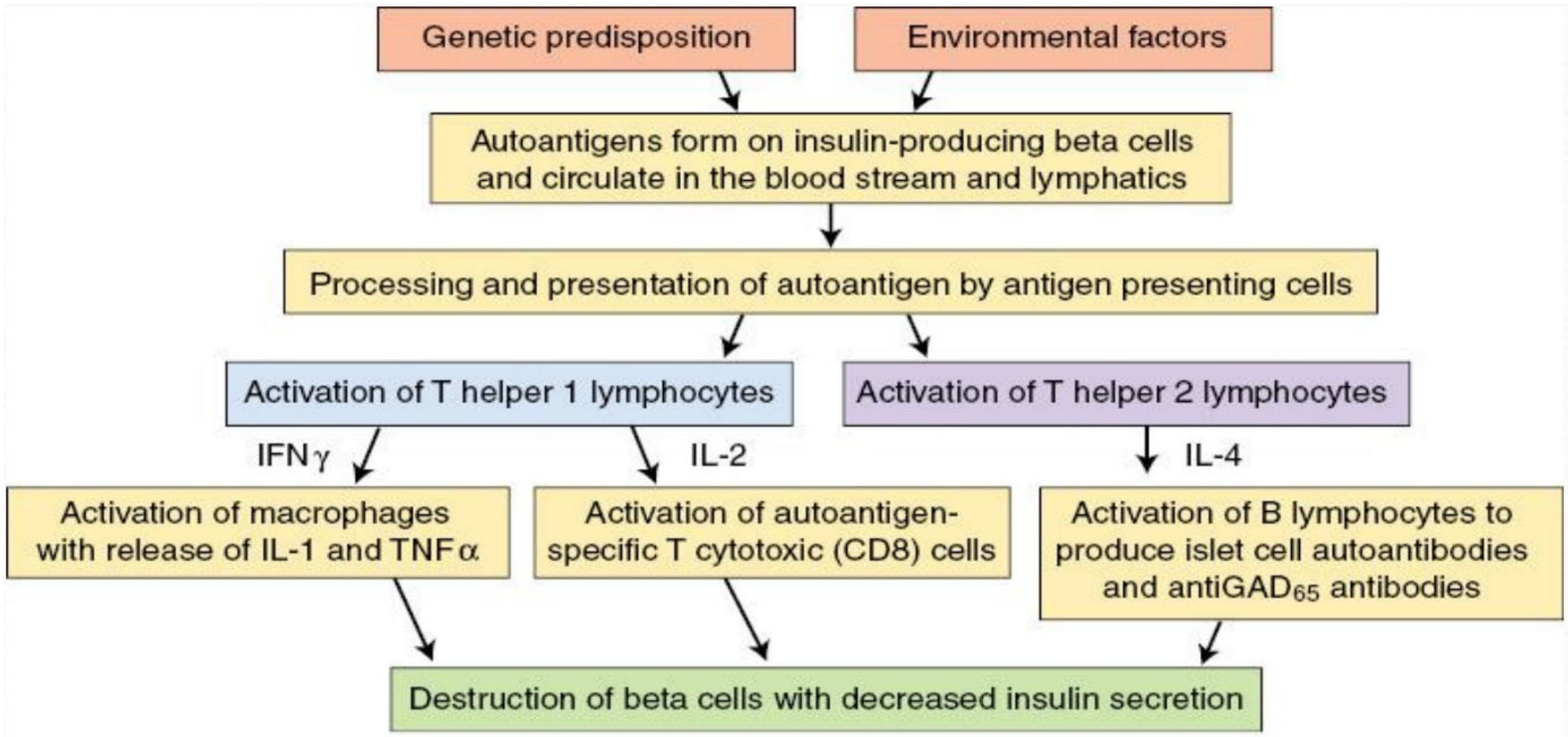
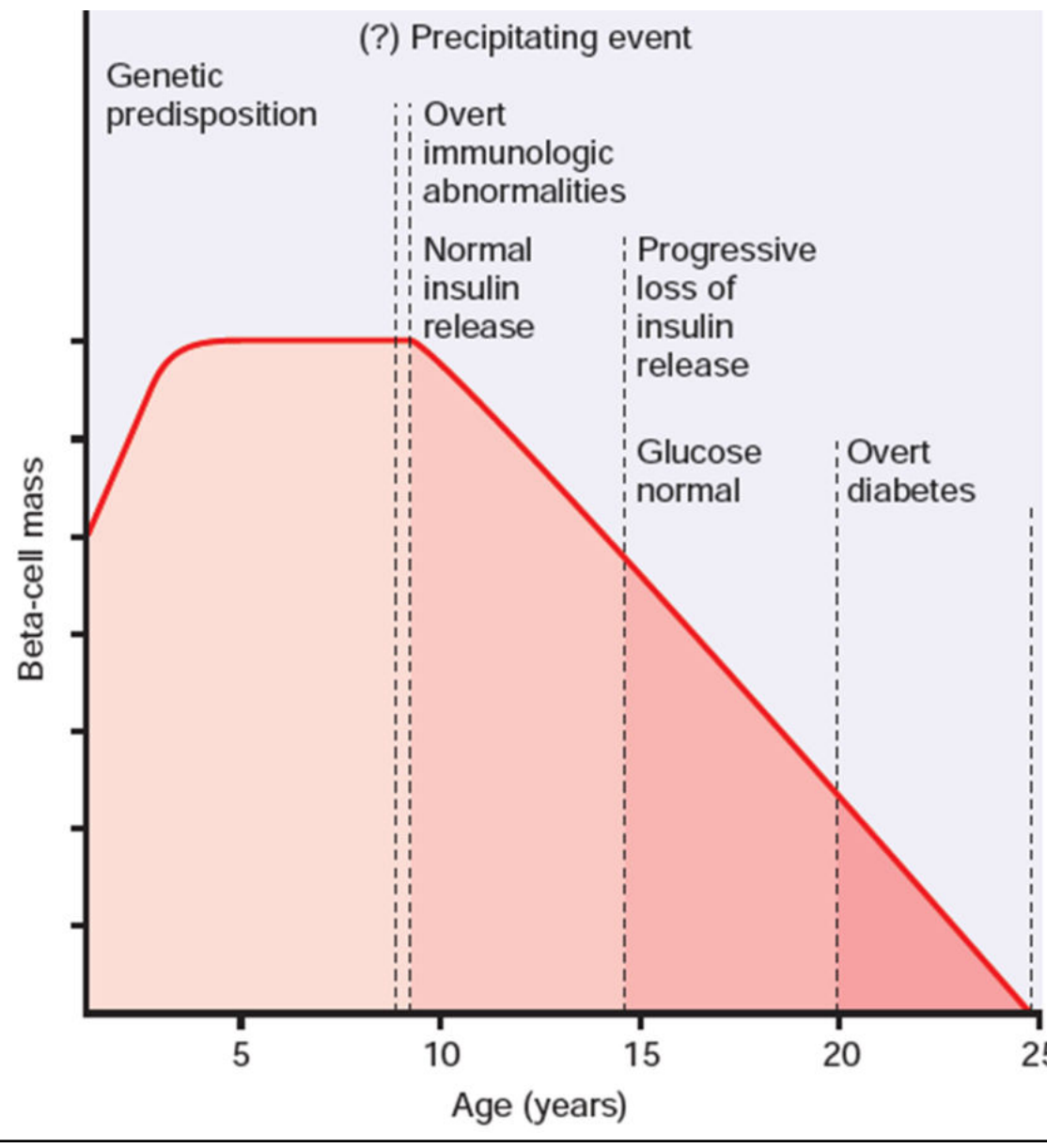


Figure 21-13 Pathophysiology of type 1 diabetes mellitus. *GAD_{65}*, glutamic acid decarboxylase; *INF*-γ Interferon-gamma; *IL*, interleukin; *TNF*-α, tumor necrosis factor-alpha.



Etiopathogenesis in DM type2

Etiology

TABLE 27.5. Major Risk Factors for Type 2 Diabetes Mellitus (ADA Recommendations, 2007).

1. Family history of type 2 DM
2. Obesity
3. Habitual physical inactivity
4. Race and ethnicity (Blacks, Asians, Pacific Islanders)
5. Previous identification of impaired fasting glucose or impaired glucose tolerance
6. History of gestational DM or delivery of baby heavier than 4 kg
7. Hypertension
8. Dyslipidaemia (HDL level < 35 mg/dl or triglycerides > 250 mg/dl)
9. Polycystic ovary disease and acanthosis nigricans
10. History of vascular disease

PATHOGENESIS OF TYPE 2 DM.

complex disease that involves an interplay of **genetic** and **environmental factors** and a **proinflammatory state**.

1-Genetic Factors-first-degree relatives have 5- to 10-fold higher risk

2-Environmental Factors-Obesity, sedentary lifestyle

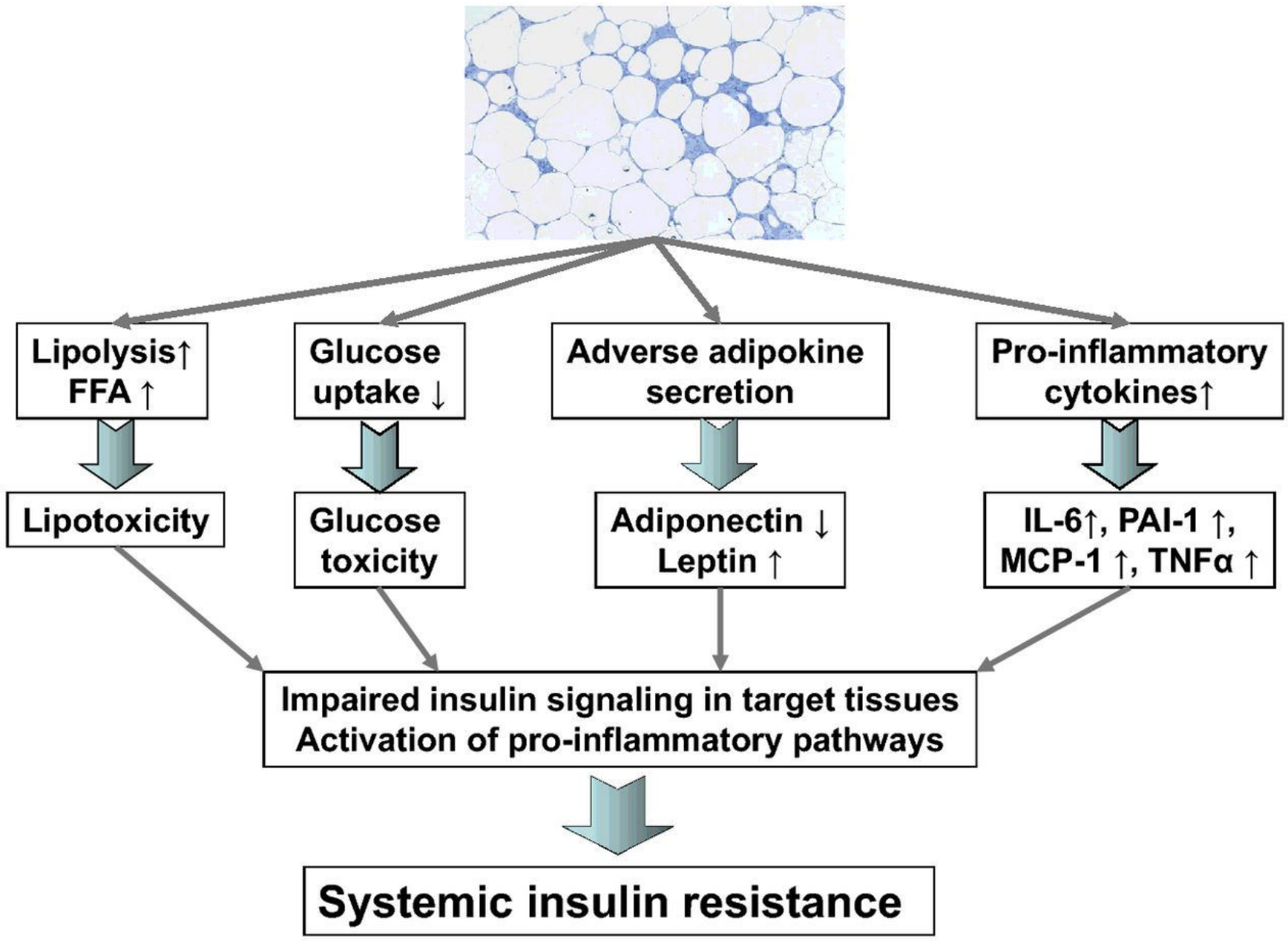
3-Insulin resistance-

Mechanism of hyperglycaemia in these cases is explained as under:

i) impairs glucose utilisation and hence hyperglycaemia.

ii) There is increased hepatic synthesis of glucose.

iii) Hyperglycaemia in obesity is related to high levels of free fatty acids and cytokines



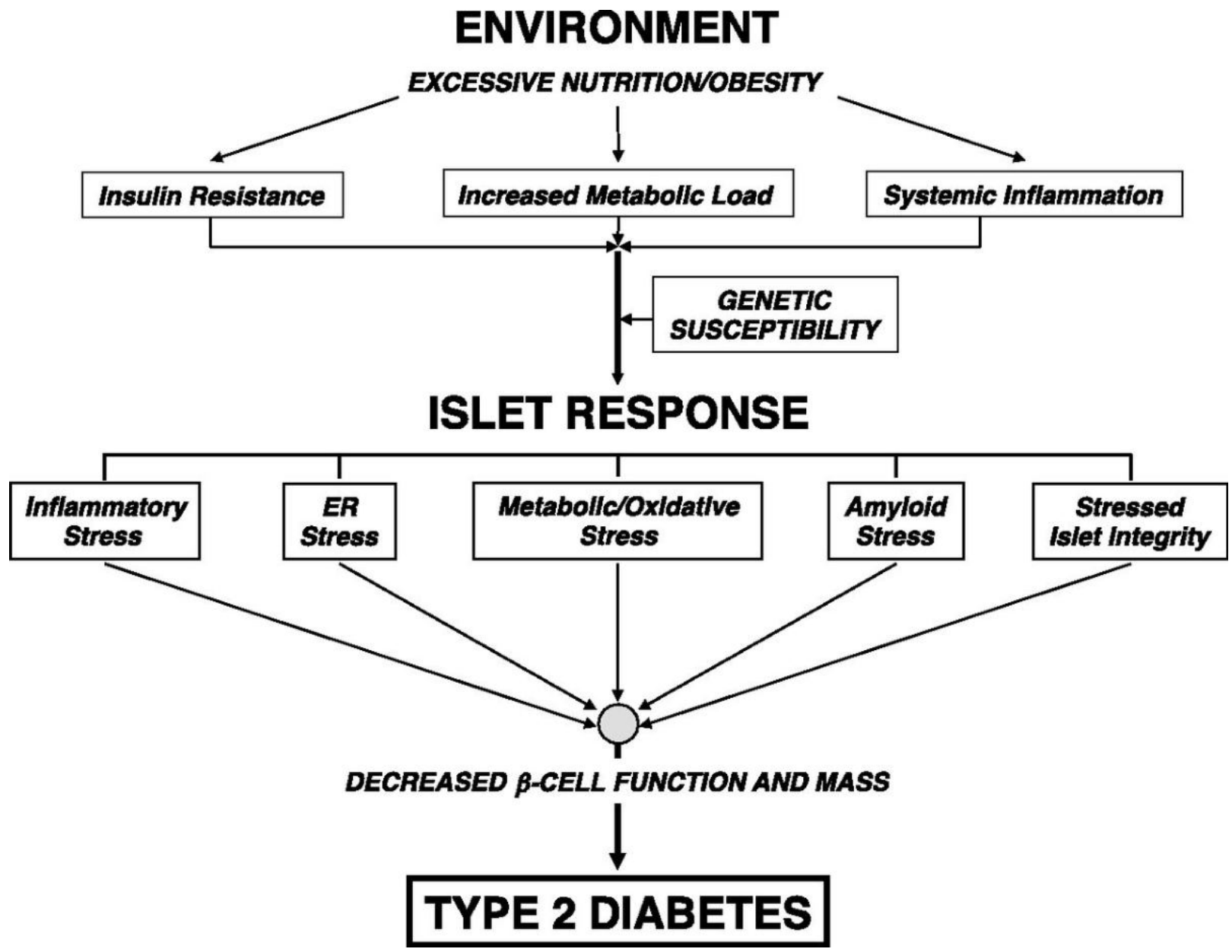
4-Current consideration-

- **Polymorphism** in various post-receptor intracellular signal pathway molecules.
- **Elevated free fatty acids**

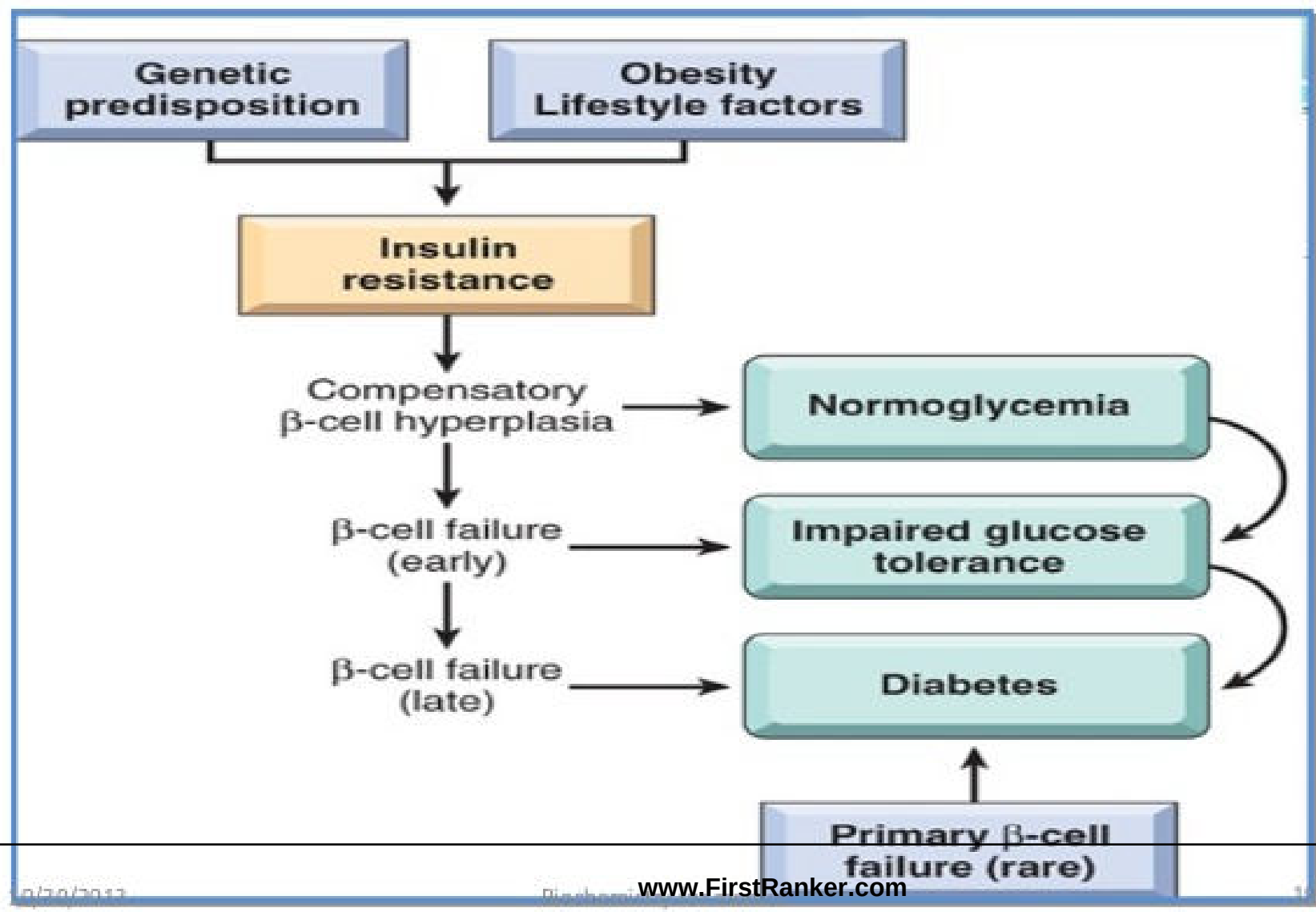
β-Cell Dysfunction

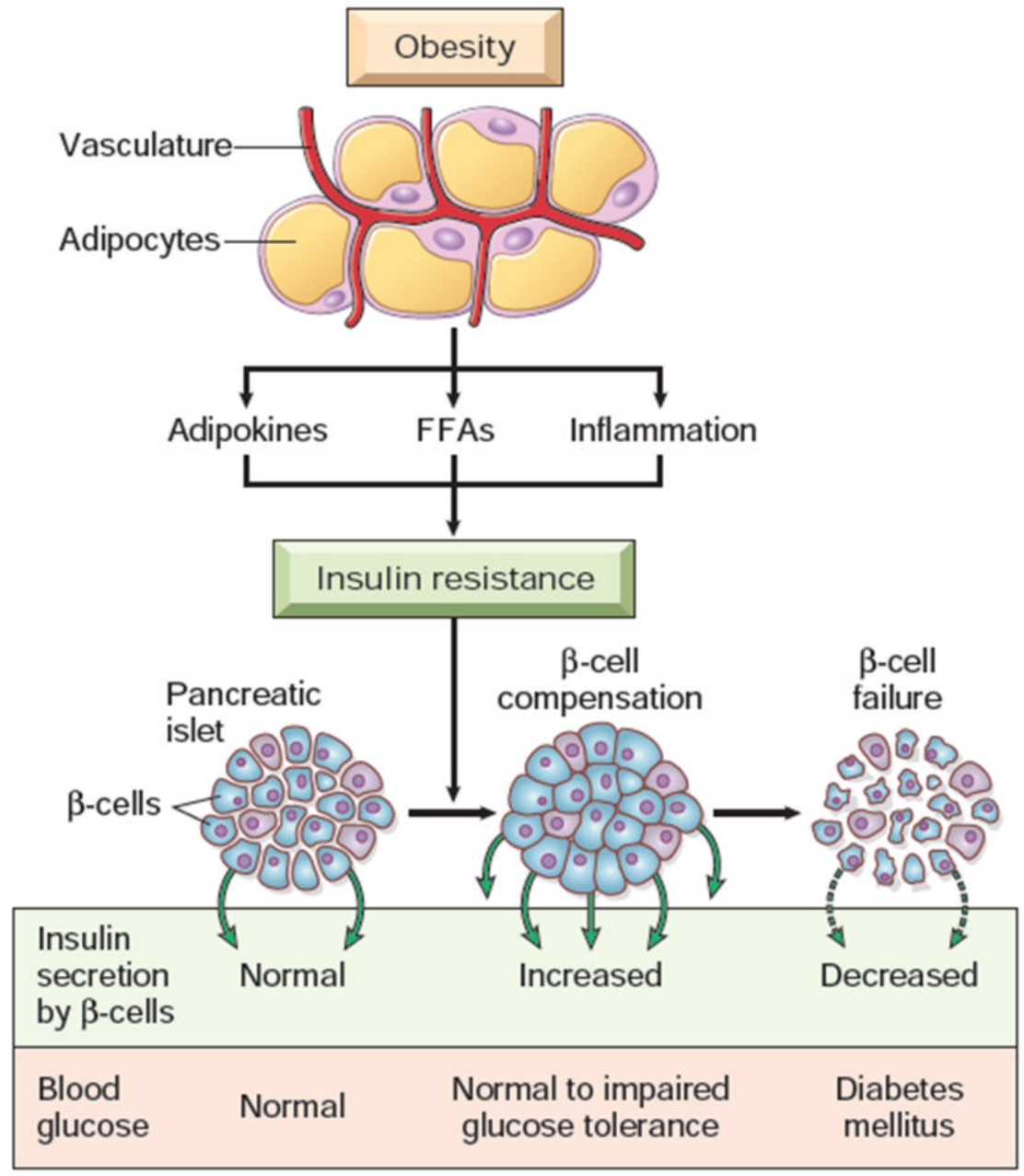
Several mechanisms have been implicated in promoting β-cell dysfunction in type 2 diabetes, including:

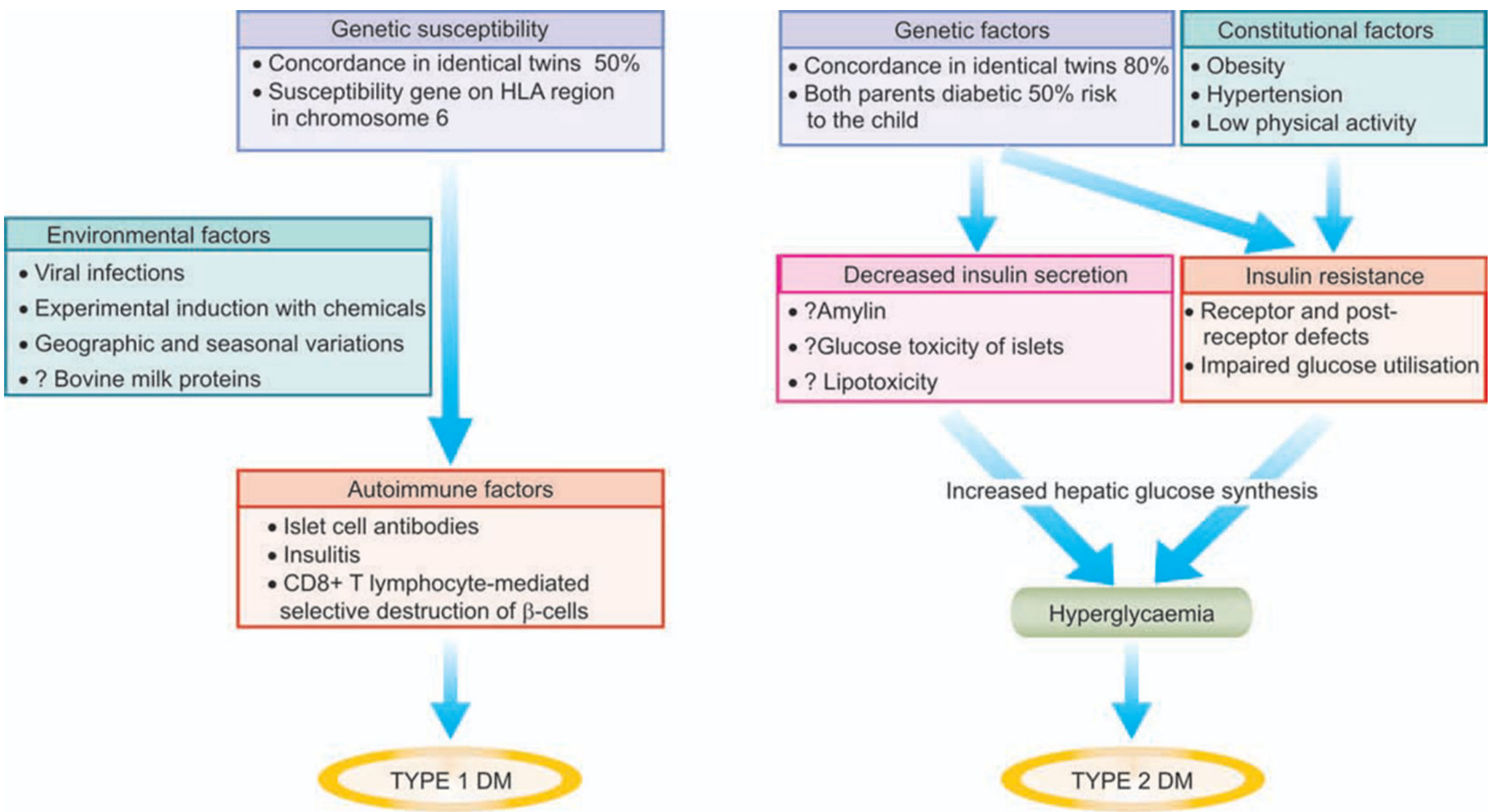
- Excess free fatty acids that compromise β cell function and attenuate insulin release (“lipotoxicity”)
- impact of chronic hyperglycemia (“glucotoxicity”)
- An abnormal “incretin effect,” leading to reduced secretion of GIP and GLP-1, hormones that promote insulin release
- Amyloid deposition within islets 90% of diabetic islets cell in long standing
- genetic predisposition



Pathophysiology of Type 2 DM







A, PATHOGENESIS OF TYPE 1 DIABETES MELLITUS B, PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Obesity and Insulin Resistance

❖Free fatty acids (FFAs)-

- accumulation of cytoplasmic intermediates like diacylglycerol (DAG)
- DAG compete with glucose for substrate oxidation

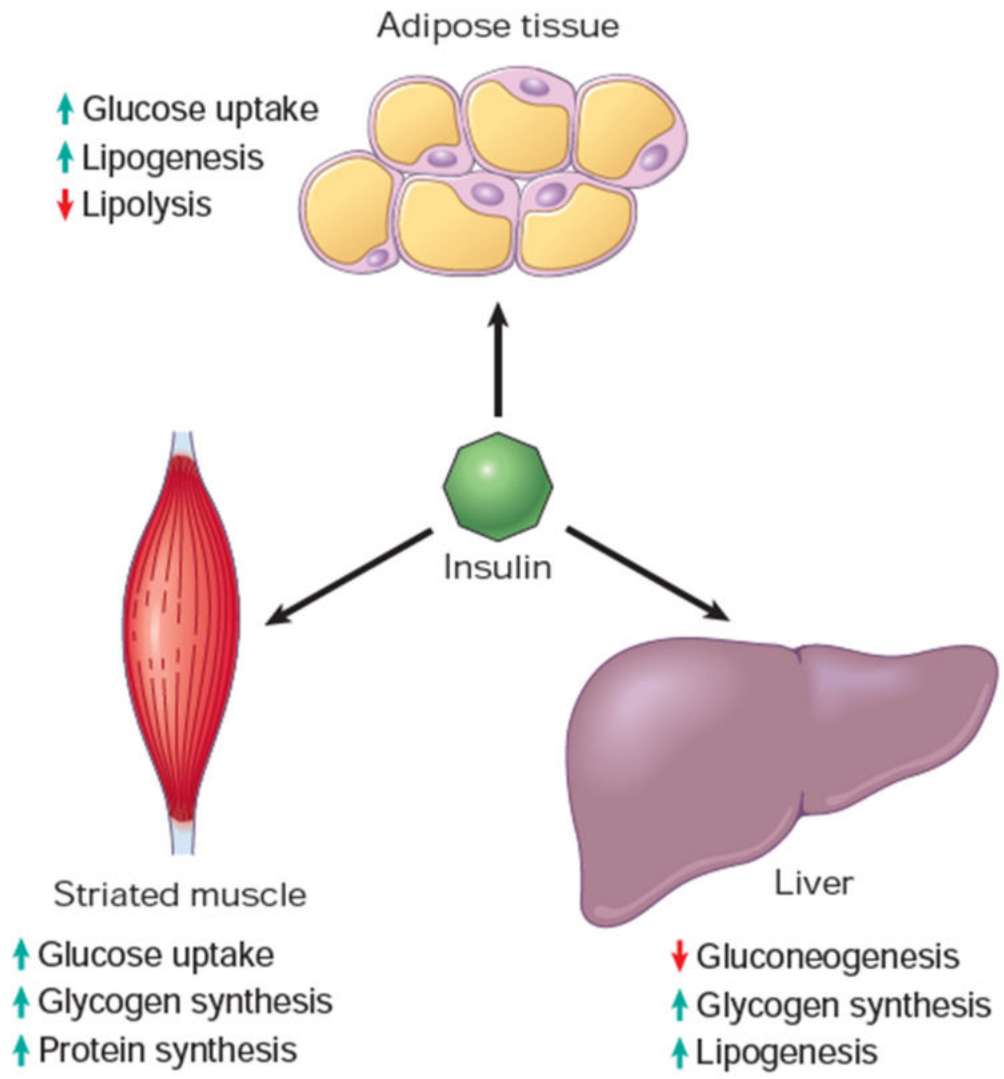
❖Adipokines- Adiponectin levels are reduced in obesity, thus contributing to insulin resistance

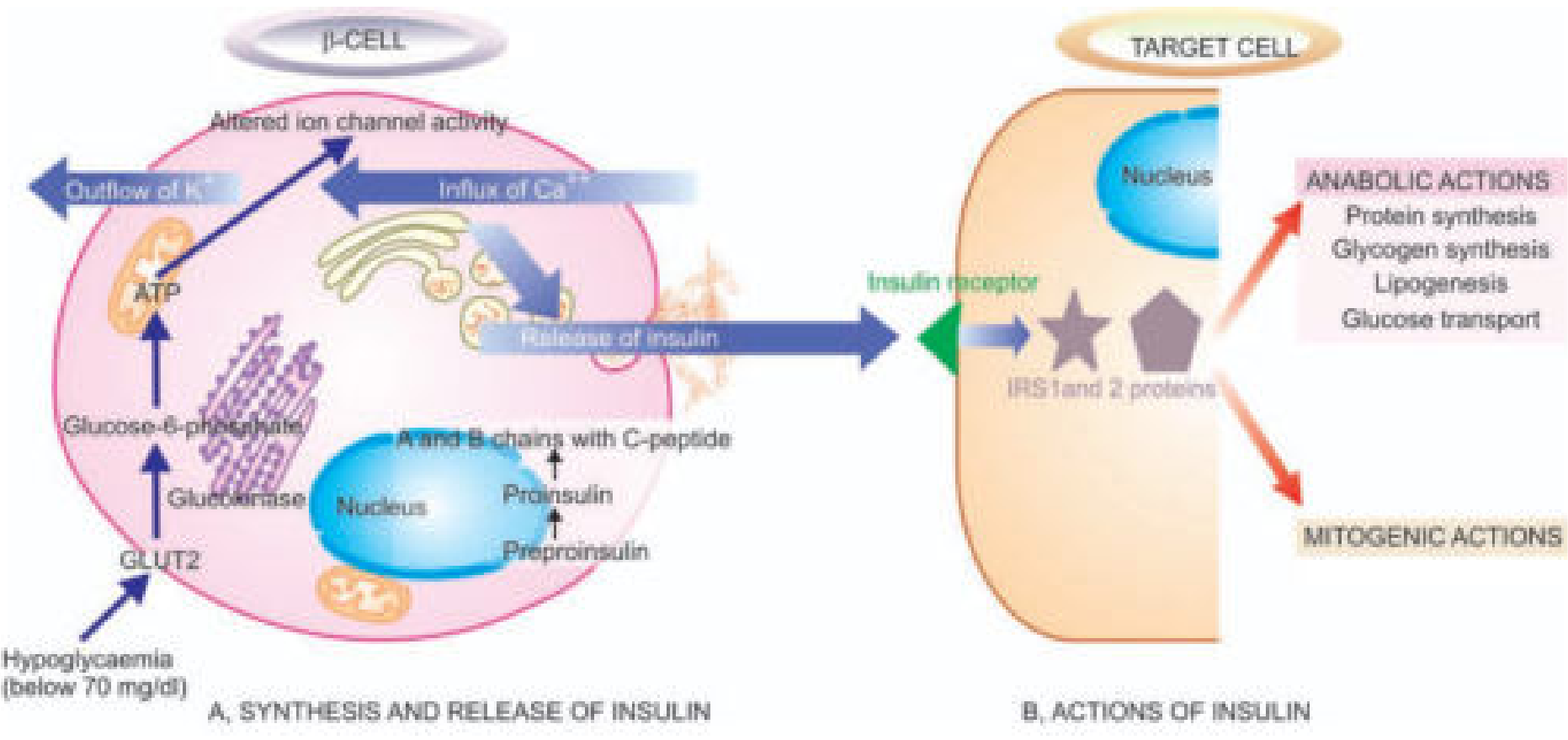
❖Inflammation

Inflammation:

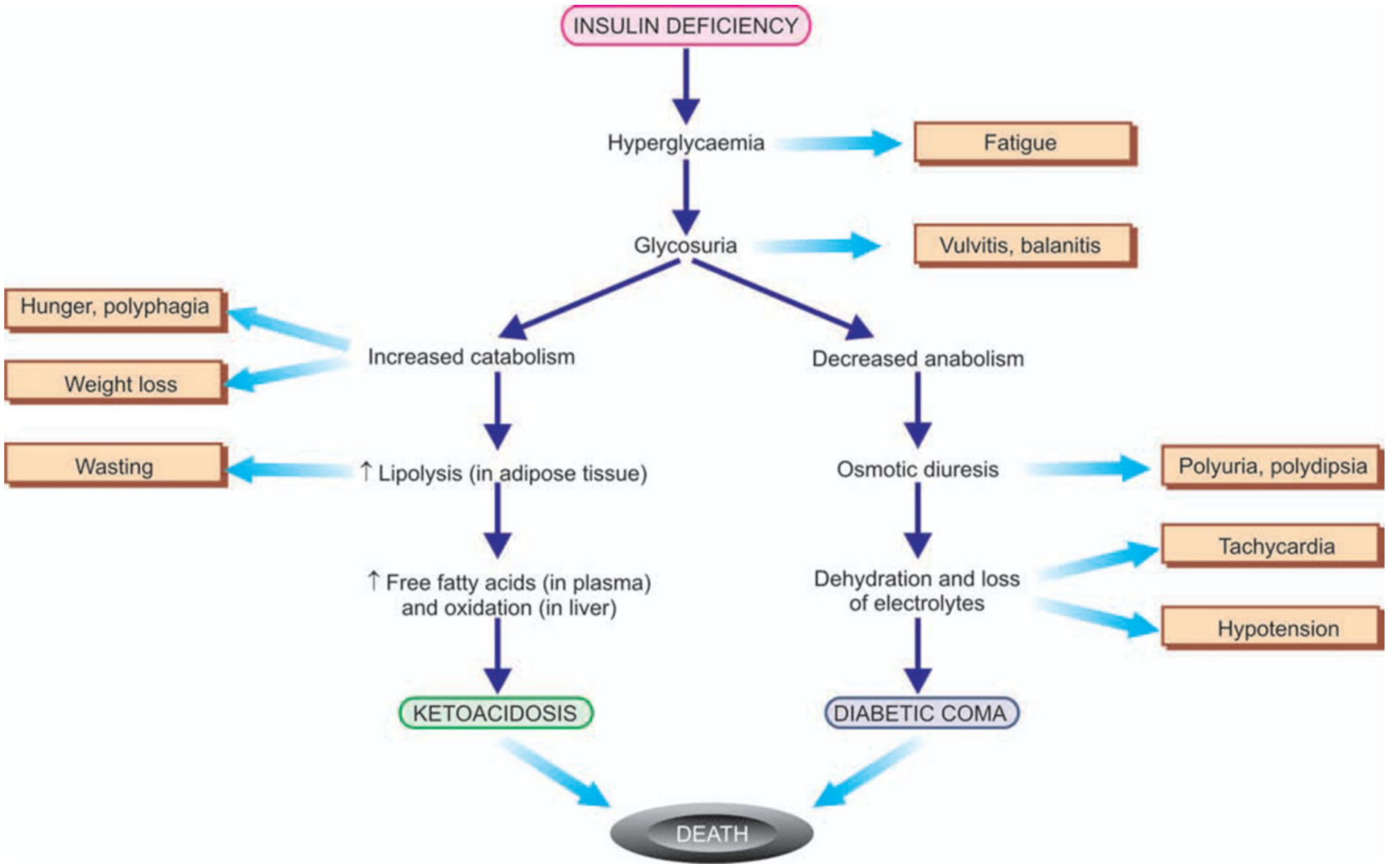
- FFA & Beta cell
- Inflammasome
- Cytokines IL-1β, IL-1
- promote insulin resistance

Metabolic actions of insulin in striated muscle, adipose tissue, and liver.





Pathophysiological basis of common signs and symptoms due to uncontrolled hyperglycaemia in diabetes mellitus



- Morphologic Features –

1. Pancreatic Islets
2. Diabetic Macrovascular Disease
3. Diabetic Microangiopathy
4. Diabetic Nephropathy
5. Diabetic Ocular Complications
6. Diabetic neuropathy

Morphologic Features

Pancreatic Islets-

1-Insulitis:

- In type 1 DM-

➢lymphocytic infiltrate,macrophage and few polymorphs

- In type 2 DM-

➢variable degree of fibrous tissue in the islets

2-Islet cell mass:

- Type-1- loss of pancreatic β−cells and its hyalinisation
- In type 2 DM-hyperplasia and hypertrophy of islets

3-Amyloidosis:

- type 1 DM- absent
- Type-2DM-around the capillaries of the islets causing compression and atrophy of islet tissue

- Diabetic Macrovascular Disease-

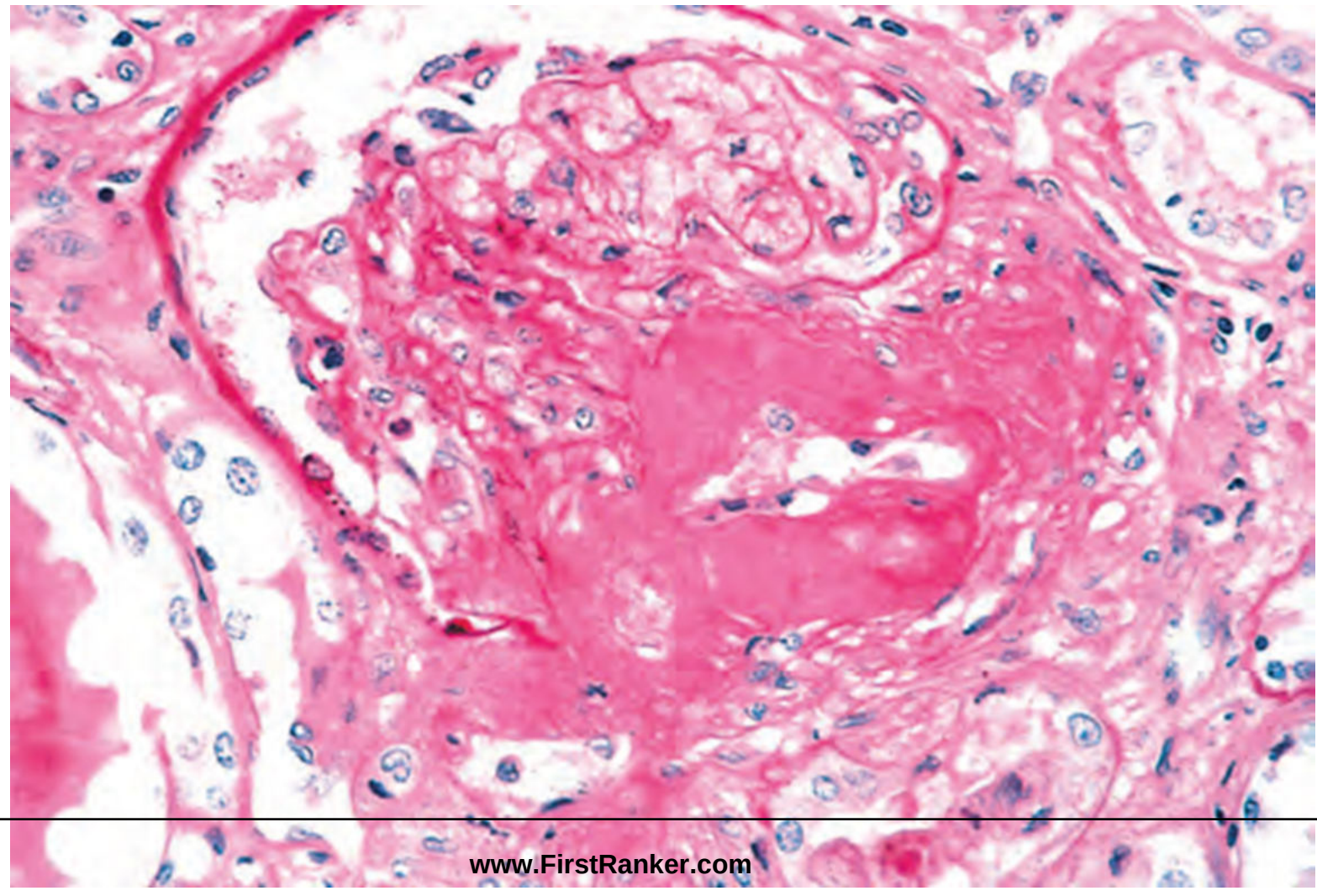
➢hallmark of diabetic macrovascular disease is accelerated atherosclerosis involving the aorta and large- and medium-sized arteries

➢Myocardial infarction

➢Gangrene of the lower extremities

➢Hyaline arteriolosclerosis

renal hyaline arteriolosclerosis



- Diabetic Microangiopathy- diffuse thickening of basement membranes.

➢capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla

➢ leaky

- Diabetic Nephropathy-

Three lesions are encountered:

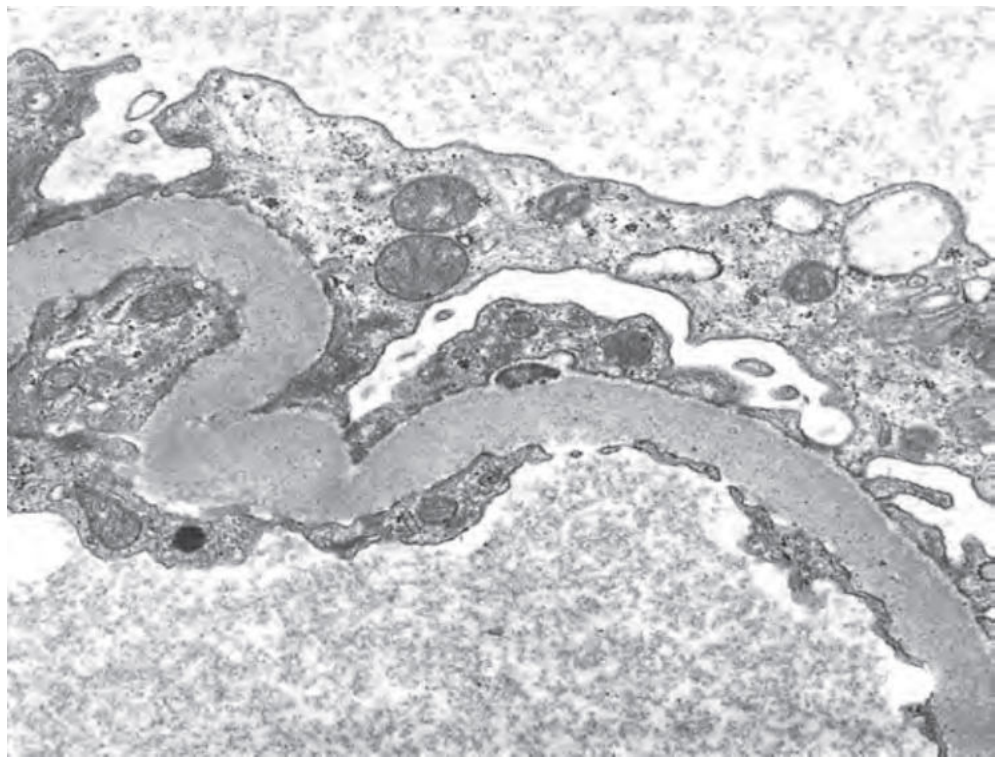
(1) glomerular lesions

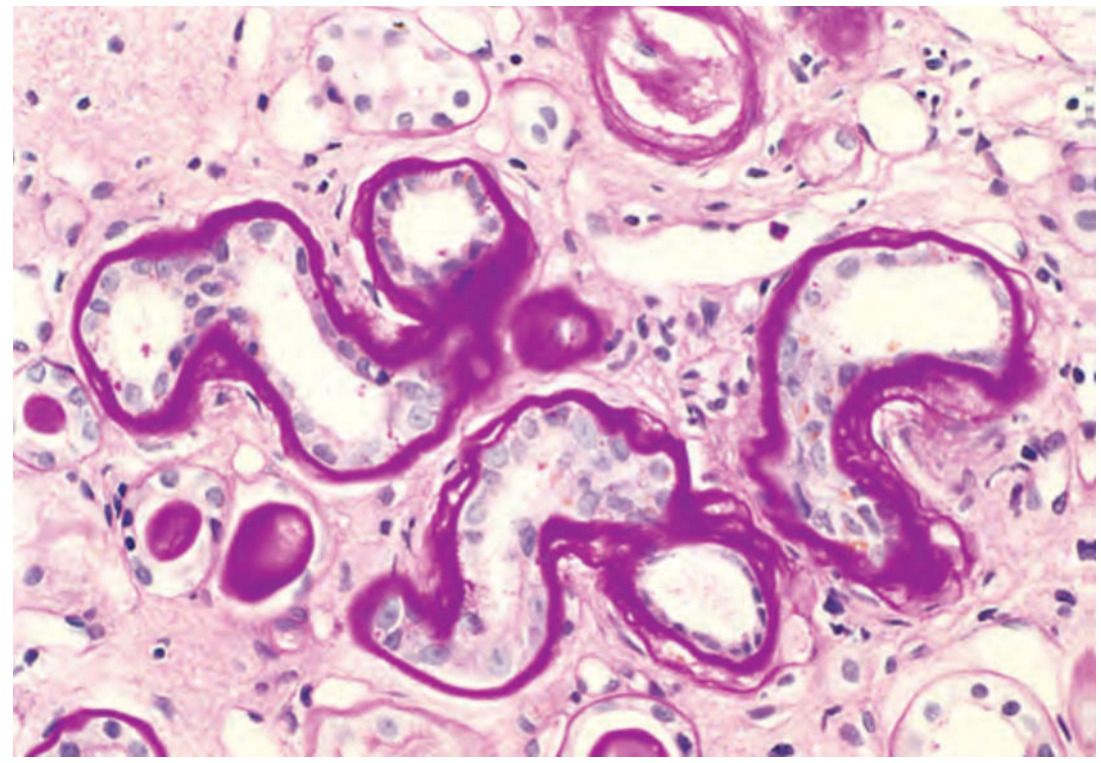
(2) renal vascular lesions

(3) pyelonephritis, including necrotizing papillitis

- Glomerular lesion-

➢Capillary Basement Membrane

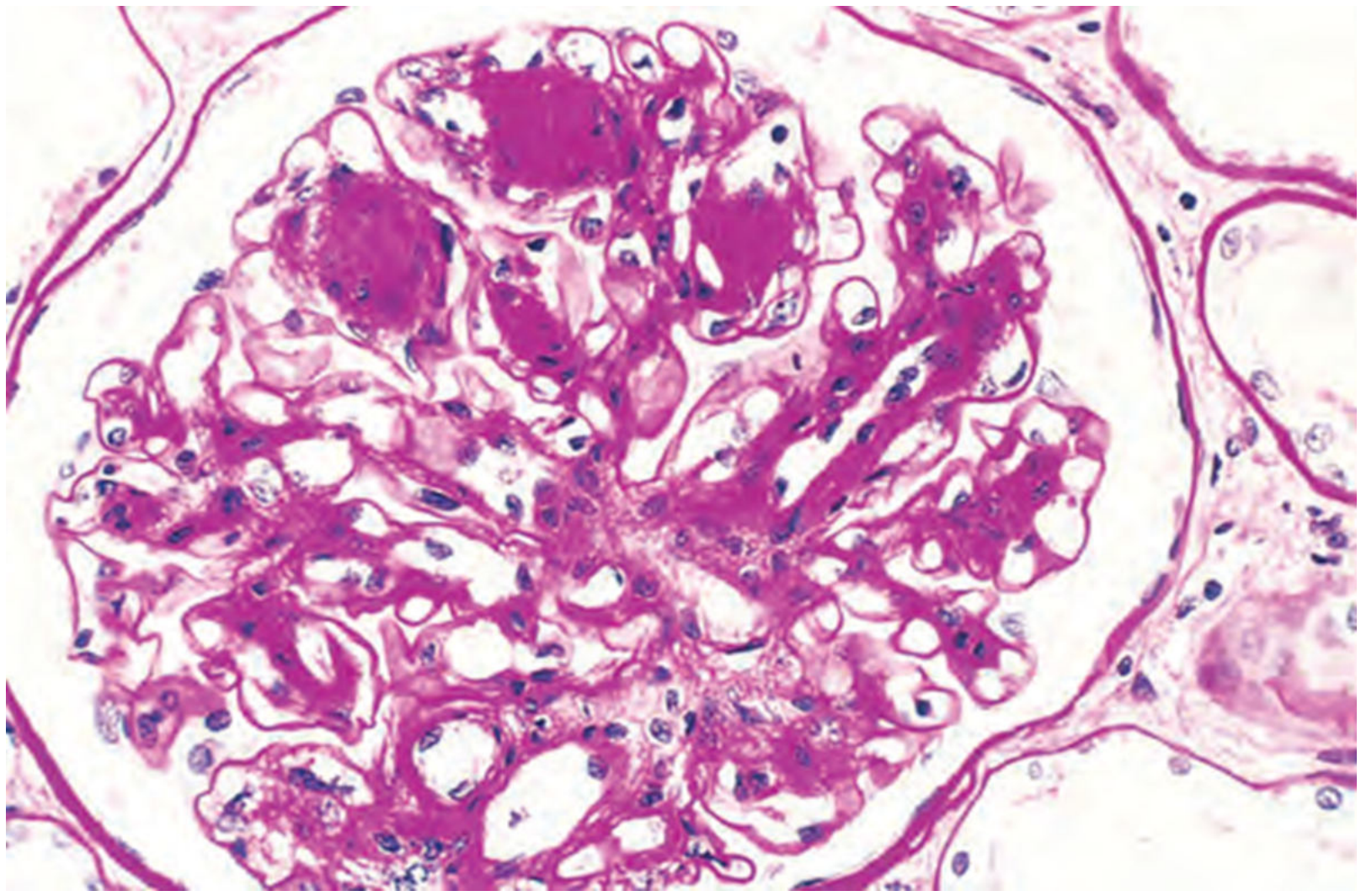




➢Diffuse Mesangial Sclerosis- consists of diffuse increase in mesangial matrix.

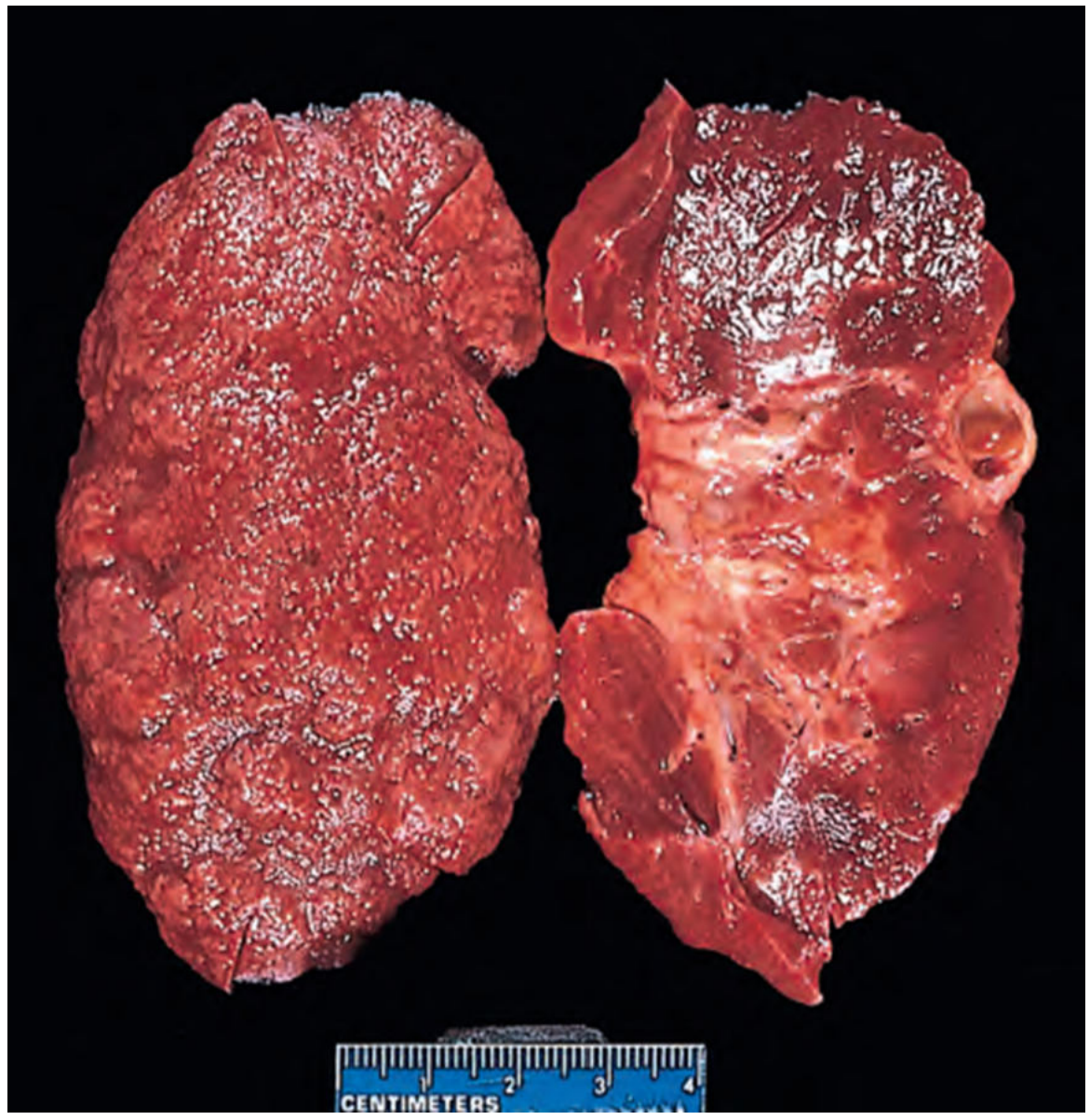
➢Nodular Glomerulosclerosis- also known as intercapillary glomerulosclerosis or Kimmelstiel-Wilson disease.

Diffuse and nodular diabetic glomerulosclerosis (PAS stain).



- nodular lesions are frequently accompanied by prominent accumulations of hyaline material in capillary loops (“fibrin caps”) or adherent to Bowman capsules (“capsular drops”).

Nephrosclerosis



- Renal atherosclerosis and arteriolosclerosis-

Hyaline arteriolosclerosis affects not only the **afferent** but also the **efferent arteriole**

- Pyelonephritis is an acute or chronic inflammation of the kidneys that usually begins in the **interstitial tissue** and then spreads to affect the **tubules**

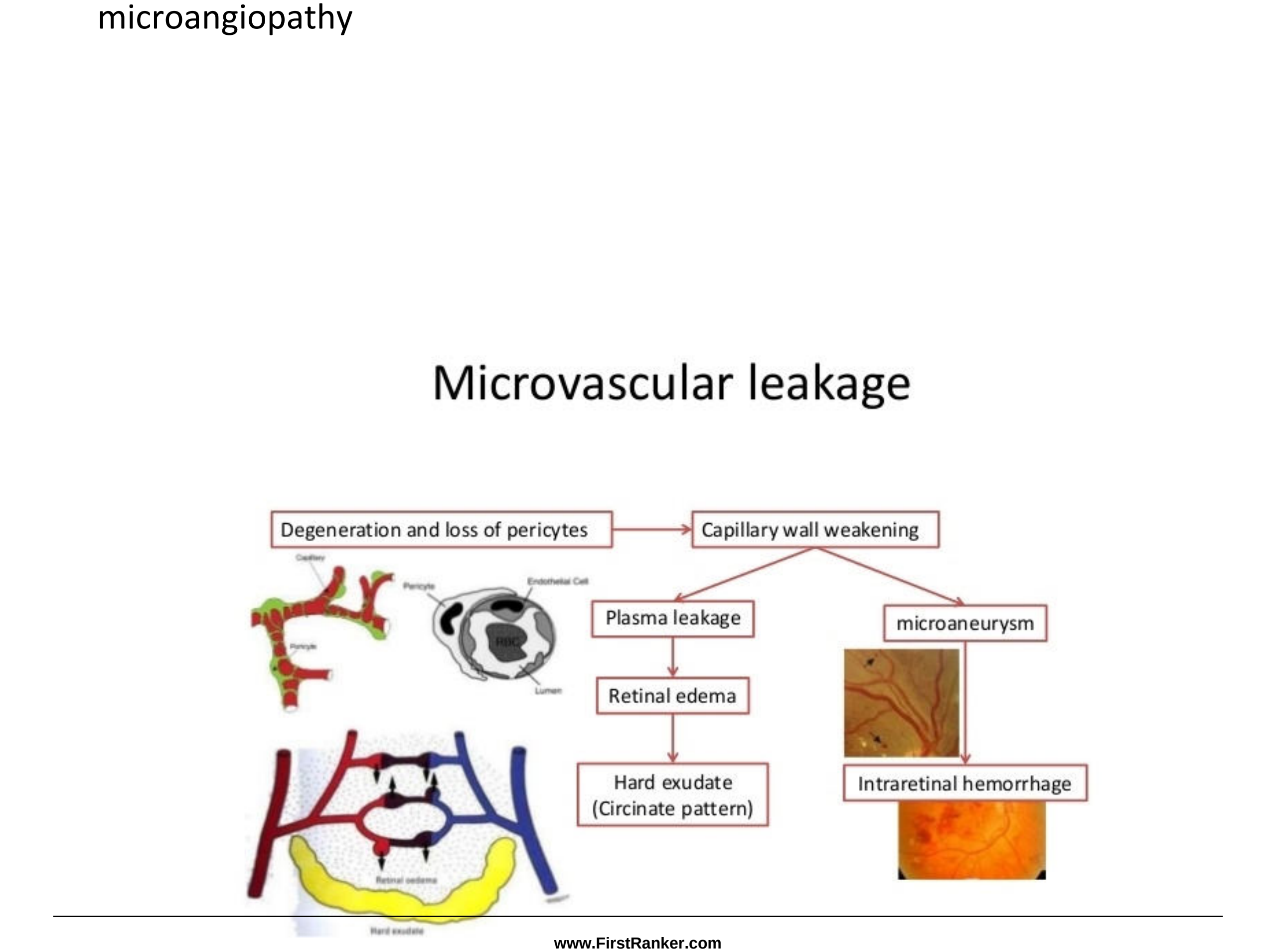
- necrotizing papillitis

Diabetic Ocular Complications-

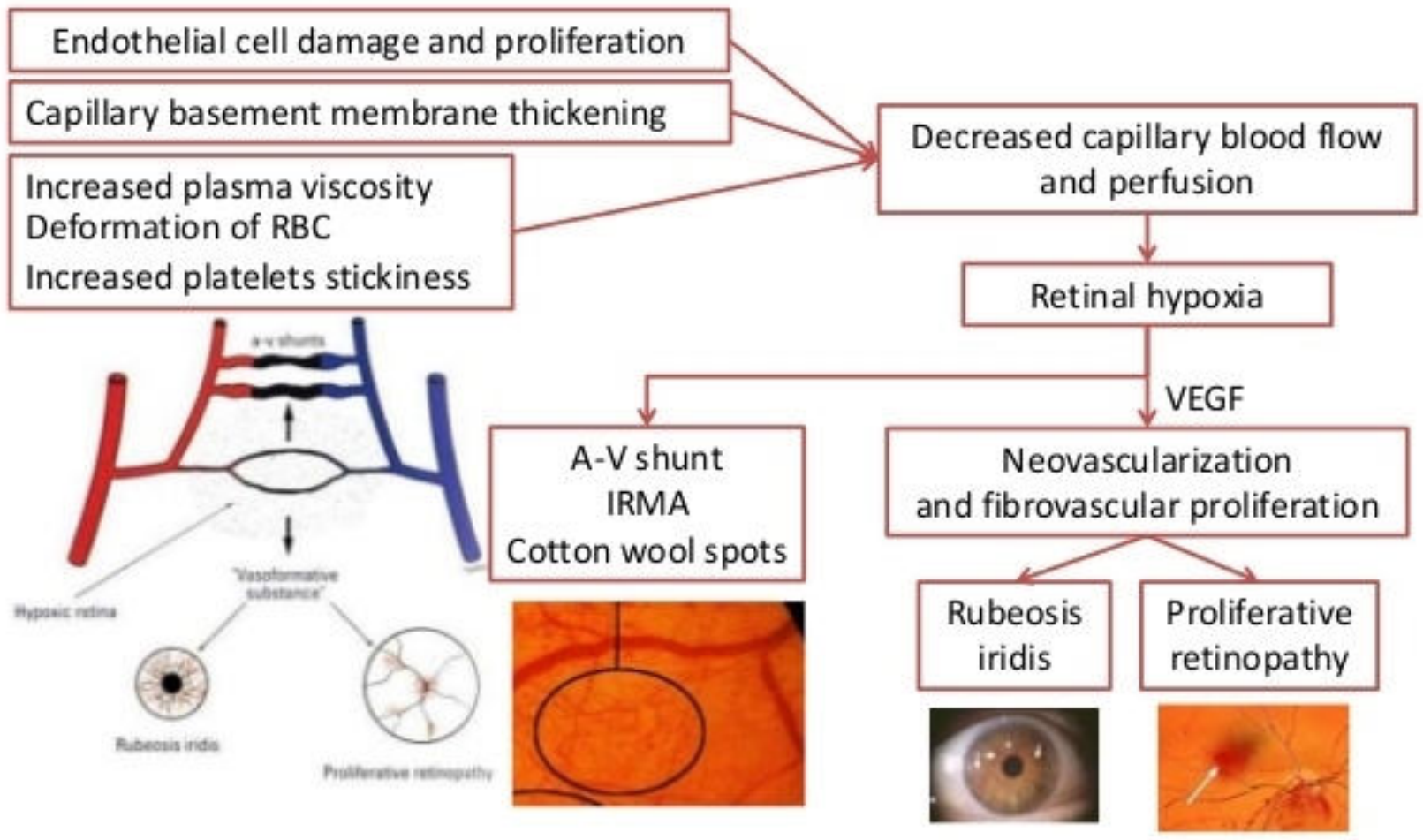
Histologically,

- Non proliferative (non-proliferative)
- proliferative retinopathy

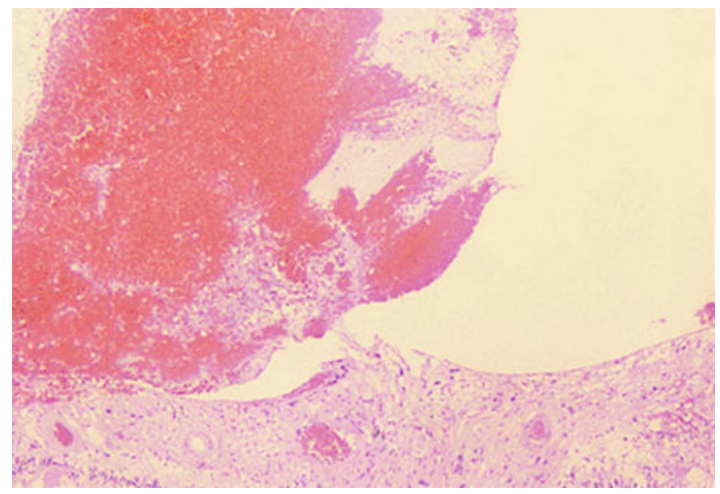
Background (non-proliferative) retinopathy. initial retinal capillary microangiopathy



Microvascular occlusion



- ii) Friability of neo vascularization results in vitreous haemorrhages.



- iii) Proliferation of astrocytes and fibrous tissue around the new blood vessels.
- iv) Fibrovascular and gliotic tissue contracts to cause retinal detachment and blindness.

- Diabetic Neuropathy-

duration of the disease; up to 50% of diabetics overall have peripheral neuropathy

Activation of PKC and polyol pathway

Accumulation of fructose and sorbitol in nerve

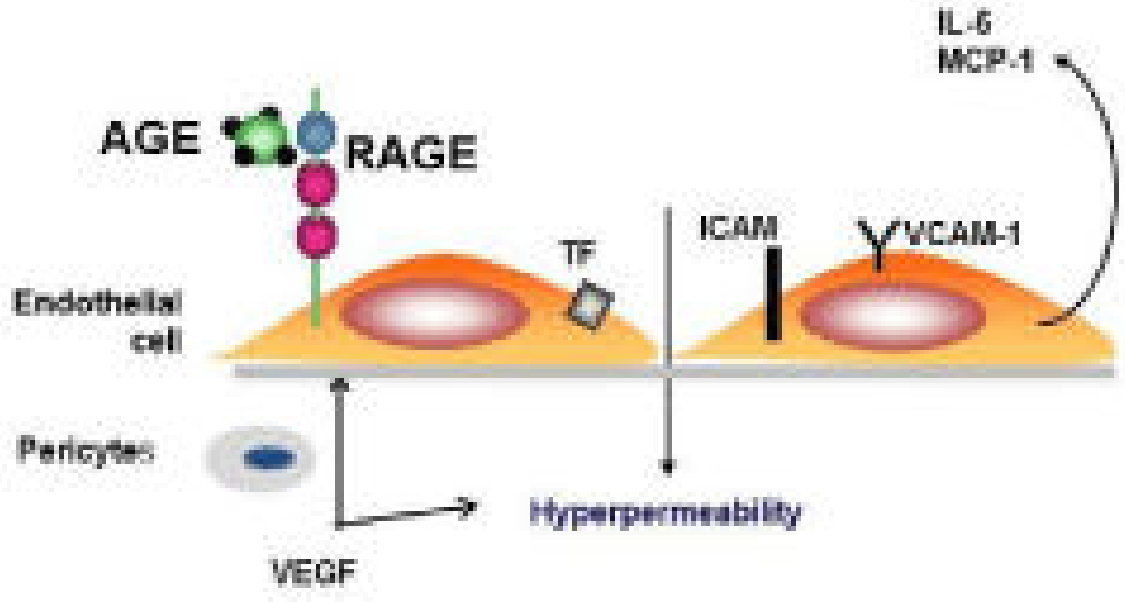
Nonenzymatic glycosylation of structural nerve protein

Four distinct mechanisms

1-Formation of Advanced Glycation End Products. *Advanced glycation end products* (**AGEs)** are formed as intracellular

glucose derived dicarbonyl precursors+ amino groups
→advanced glycation end product(AGEs)
(glyoxal, methylglyoxal, and 3-deoxyglucosone)

- AGEs bind to a specific receptor (**RAGE)** that is expressed on inflammatory cells (macrophages and T cells), endothelium, and vascular smooth muscle.



AGE-RAGE signalling axis

- TGFβ-**excess basement membrane material**
- *vascular endothelial growth factor* (VEGF)- neovasculerization
- reactive oxygen species (ROS) in endothelial cells
- procoagulant activity
- Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix

2-Activation of Protein Kinase C.

second messenger diacyl glycerol (DAG) is an important signal transduction pathway.

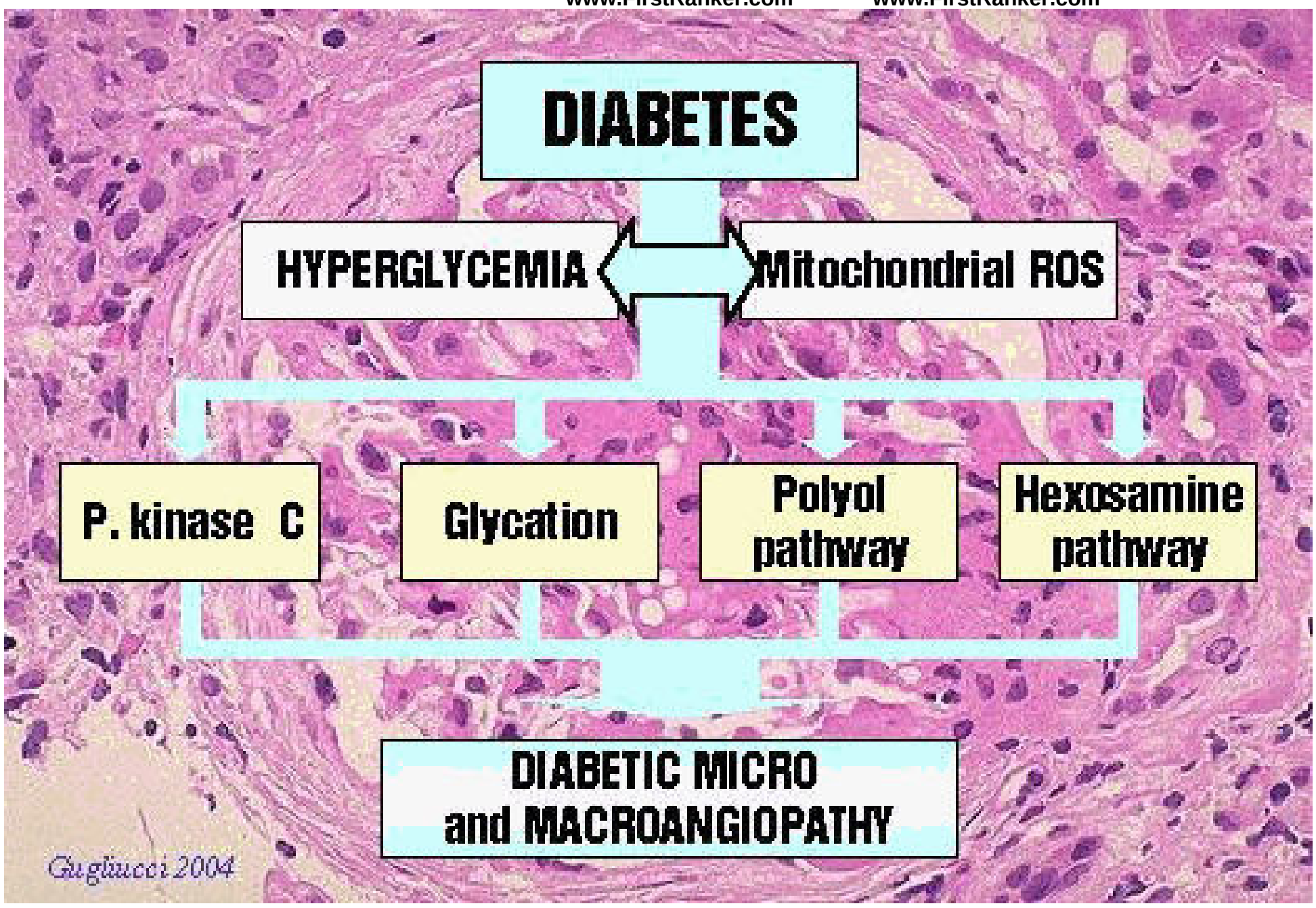
Intracellular hyperglycemia---→ *de novo* synthesis of DAG--→excessive PKC activation-→ vascular permeability and angiogenesis

3-Oxidative Stress and Disturbances in Polyol Pathways

- Sustained hyperglycemia---- aldol reductase-- progressive depletion of intracellular NADPH --→ decreased rgeneration of reduced glutathione(GSH) -→ increasing cellular susceptibility to oxidative stress
- *Responsible for diabetic neuropathy*

4-Hexosamine Pathways and Generation of Fructose-6- Phosphate

Hyperglycemia ---→increases intracellular levels of *fructose-6-phosphate via HM-→ excess proteoglycans* -→ abnormal expression of TGFβ or PAI-1---→ exacerbate the end-organ damage



Complications of Diabetes-

I.Acute metabolic complications:

- diabetic ketoacidosis
- hyperosmolar nonketotic coma
- hypoglycaemia

II. Late systemic complications:

- atherosclerosis
- diabetic microangiopathy
- diabetic nephropathy
- diabetic neuropathy
- diabetic retinopathy and infections

1.Diabetic ketoacidosis (DKA), complication of type 1 DM.

Lack of insulin

↓

Lypolysis

↓

Free fatty acid in plasma

↓

FFA+acetyl co enzyme A--→liver → Ketone body

2.Hyperosmolar hyperglycaemic nonketotic coma (HHS)-

High Blood sugar

↓

High plasma osmolality

↓

Hyperglycemic diuresis

↓

Dehydrartion

↓

CNS complication

3.Hypoglycaemia-

- patients of type 1 DM.
- Excessive administration of insulin, missing a meal, or due to stress

II.LATE SYSTEMIC COMPLICATIONS-

1.Atherosclerosis-

- hyperlipidaemia,
- reduced HDL levels,
- nonenzymatic glycosylation,
- increased platelet adhesiveness,
- obesity
- hypertension

2.Diabetic microangiopathy

3. Diabetic nephropathy

4. Diabetic neuropathy

5. Diabetic retinopathy

6. Infections-

- impaired leucocyte functions
- reduced cellular immunity
- poor blood supply