Diabetes Mellitus

DR. AMIT YELE

MBBS,

MD (Medicine),

DNB (Medicine),

PGDGM,

EULAR Fellowship,

Diabetology fellowship,

PGDHHM.

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

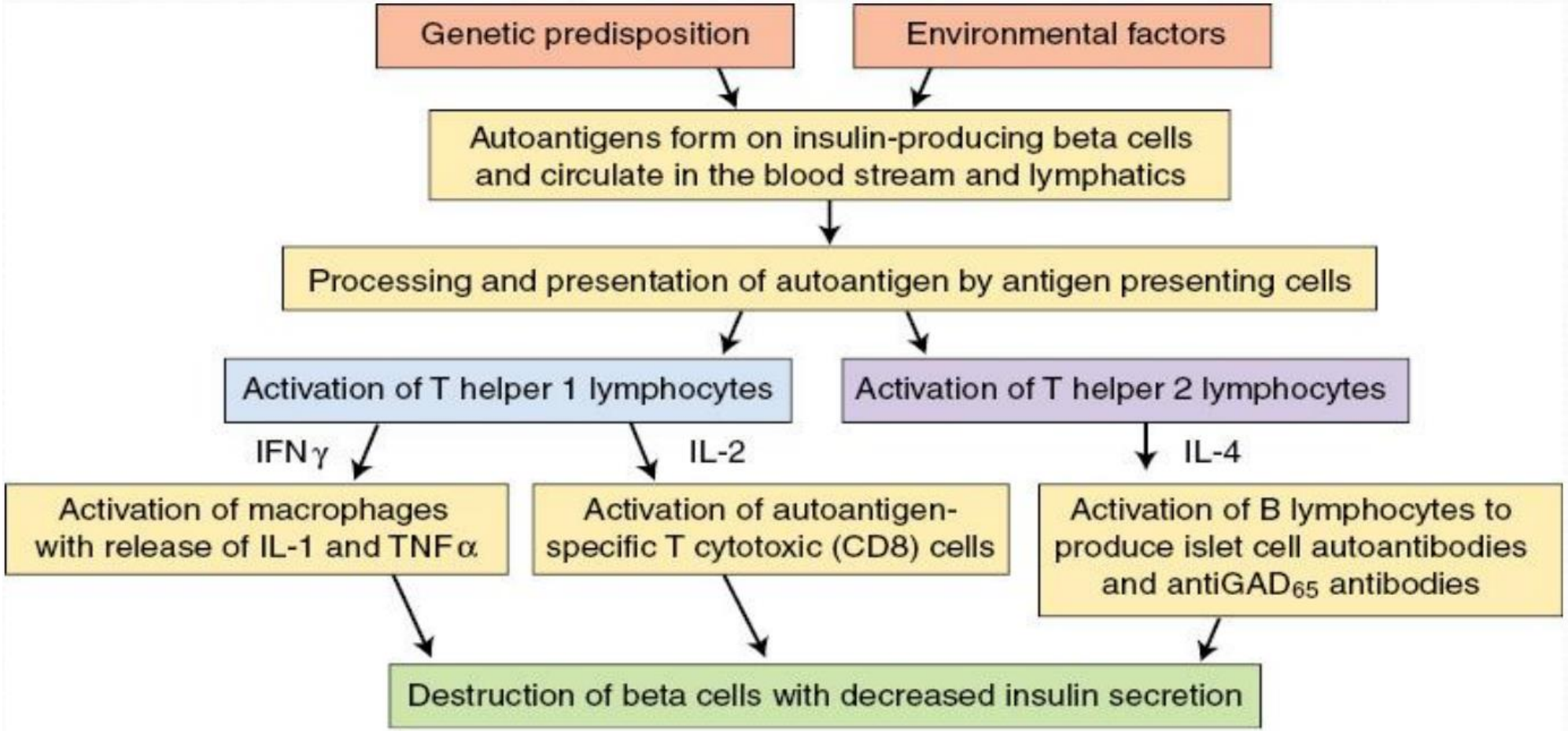
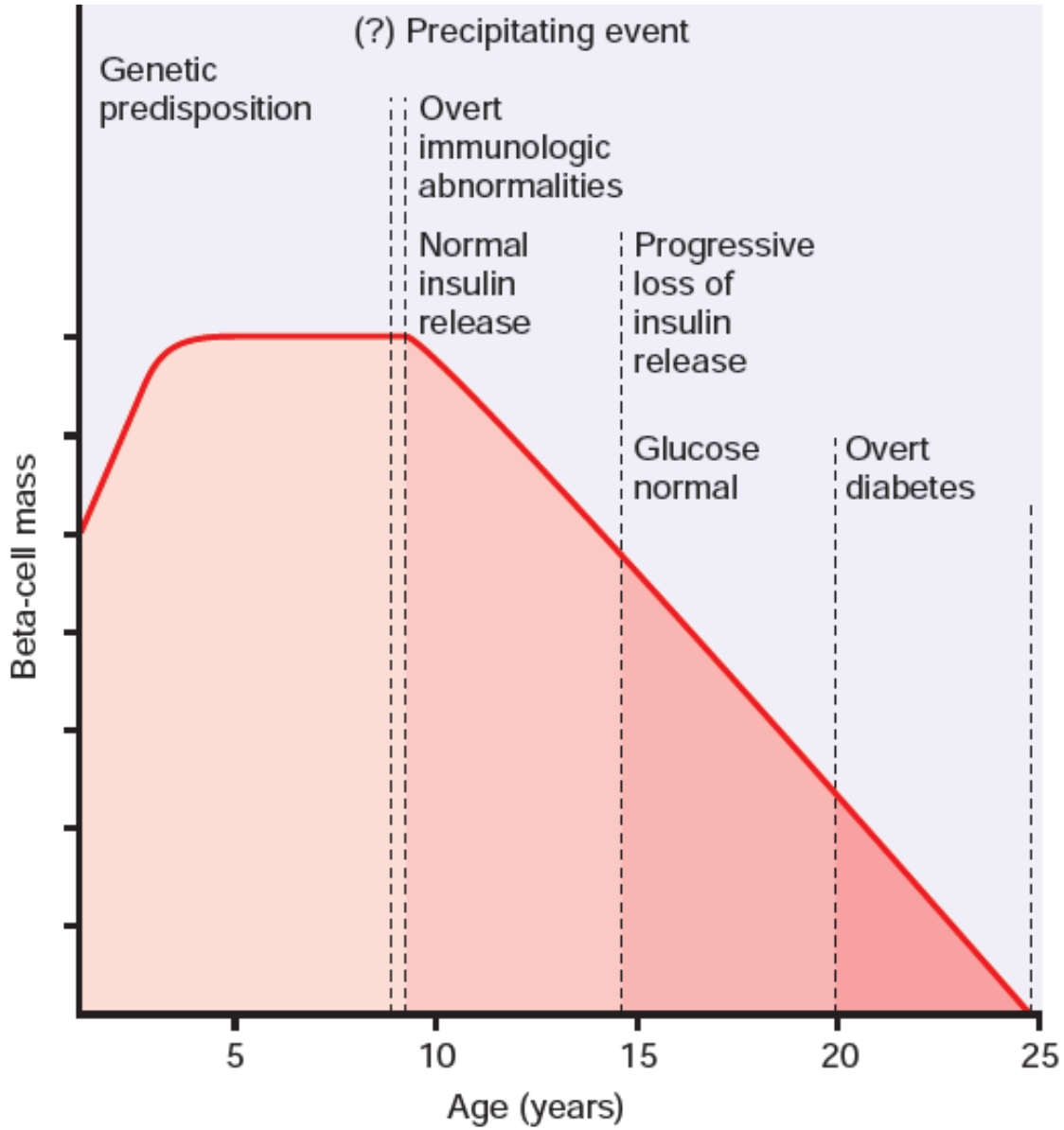


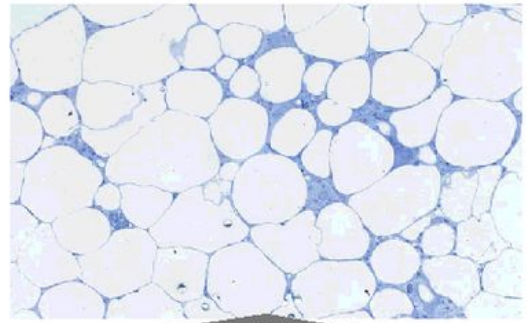
Figure 21-13 Pathophysiology of type 1 diabetes mellitus. *GAD_{65},* glutamic acid decarboxylase; *INF*-γ Interferon-gamma; *IL,* interleukin; *TNF*-α, tumor necrosis factor-alpha.


(?) Precipitating event
Genetic predisposition
Overt immunologic abnormalities
Normal insulin release
Progressive loss of insulin release
Glucose normal
Overt diabetes
Beta-cell mass
5
10
15
20
25
Age (years)

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



Lipolysis↑
FFA ↑

Glucose
uptake ↓

Adverse adipokine
secretion

Pro-inflammatory
cytokines↑

Lipotoxicity

Glucose
toxicity

Adiponectin ↓
Leptin ↑

IL-6↑, PAI-1 ↑,
MCP-1 ↑, TNFα ↑

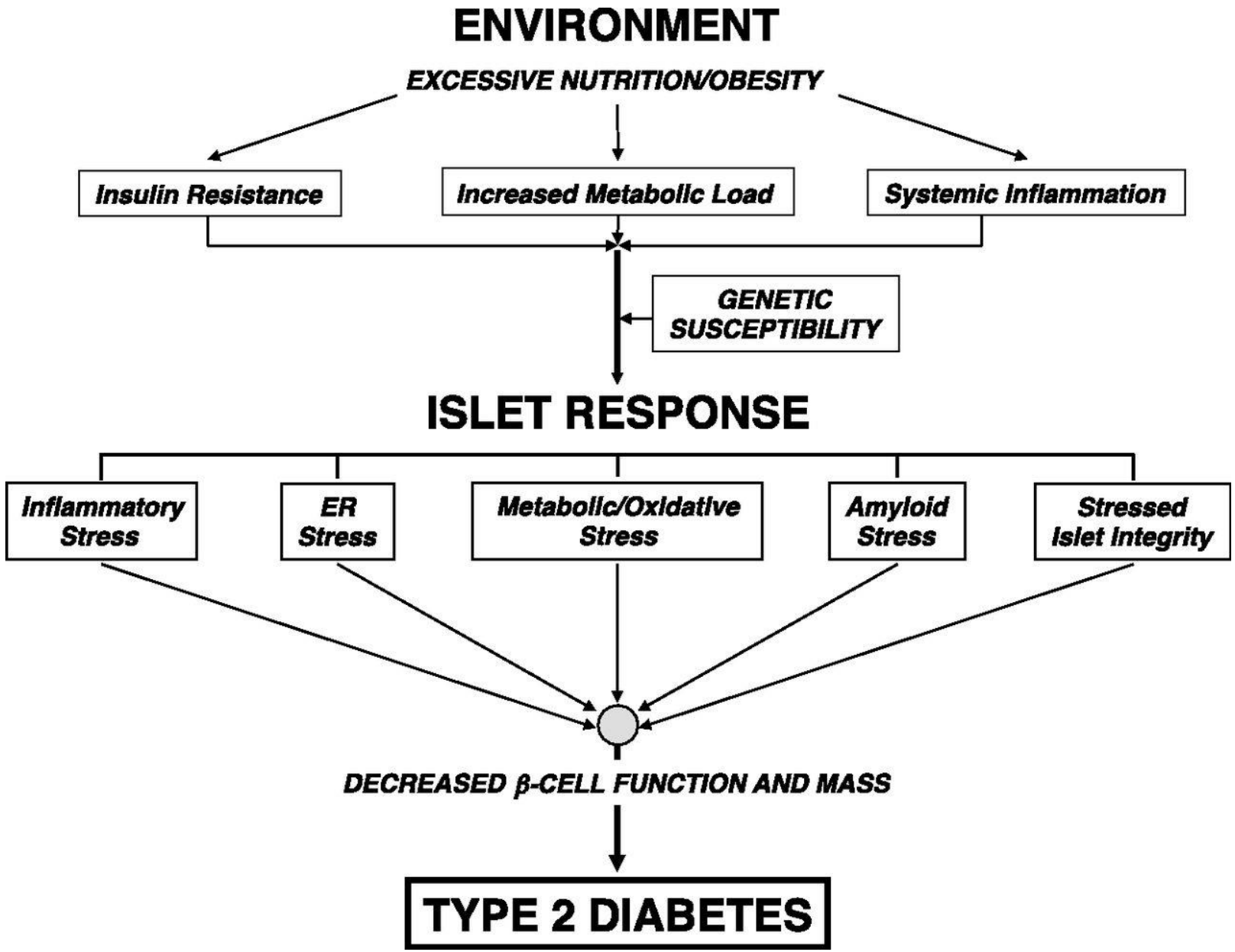
Impaired insulin signaling in target tissues
Activation of pro-inflammatory pathways

Systemic insulin resistance

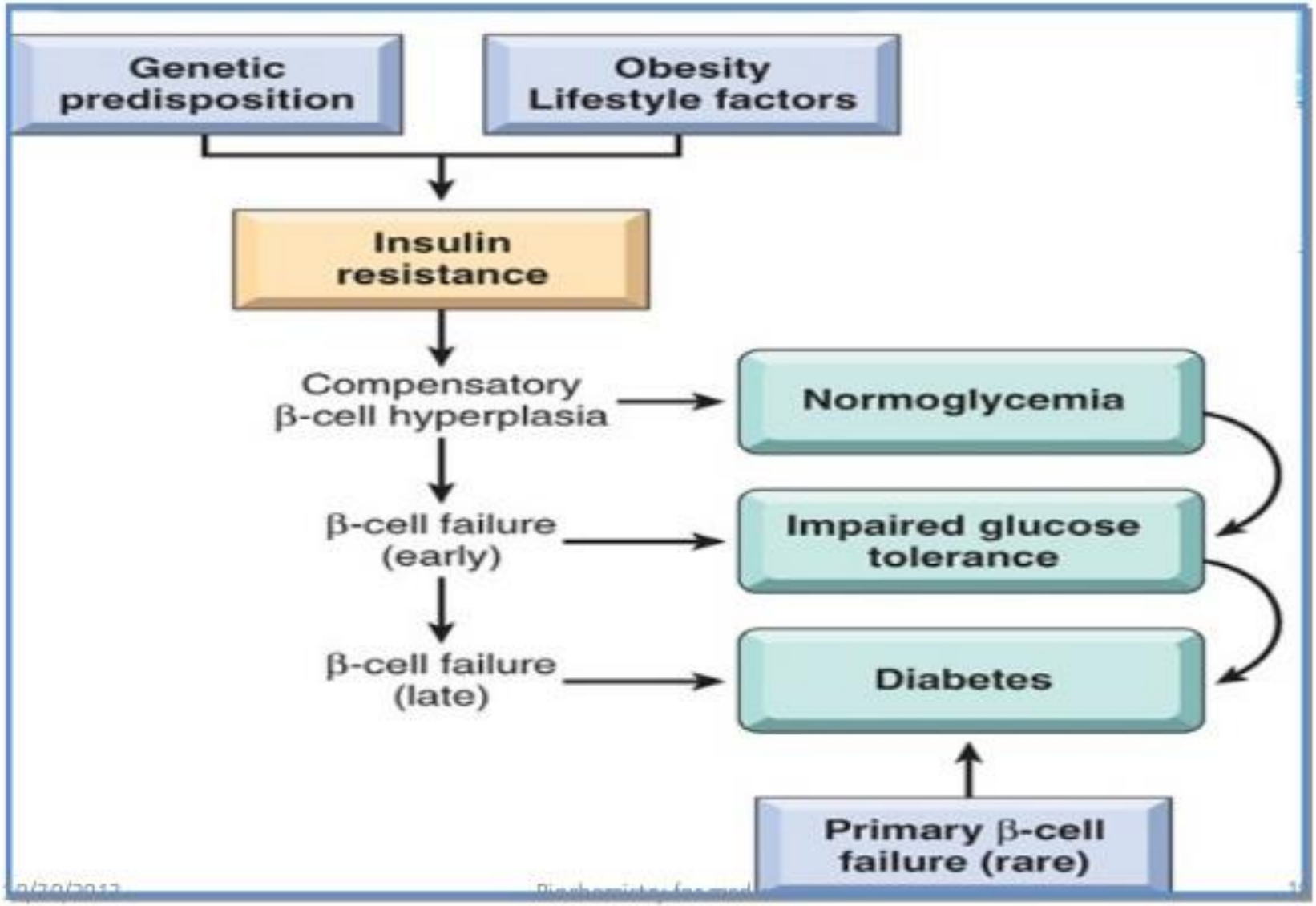
β-Cell Dysfunction

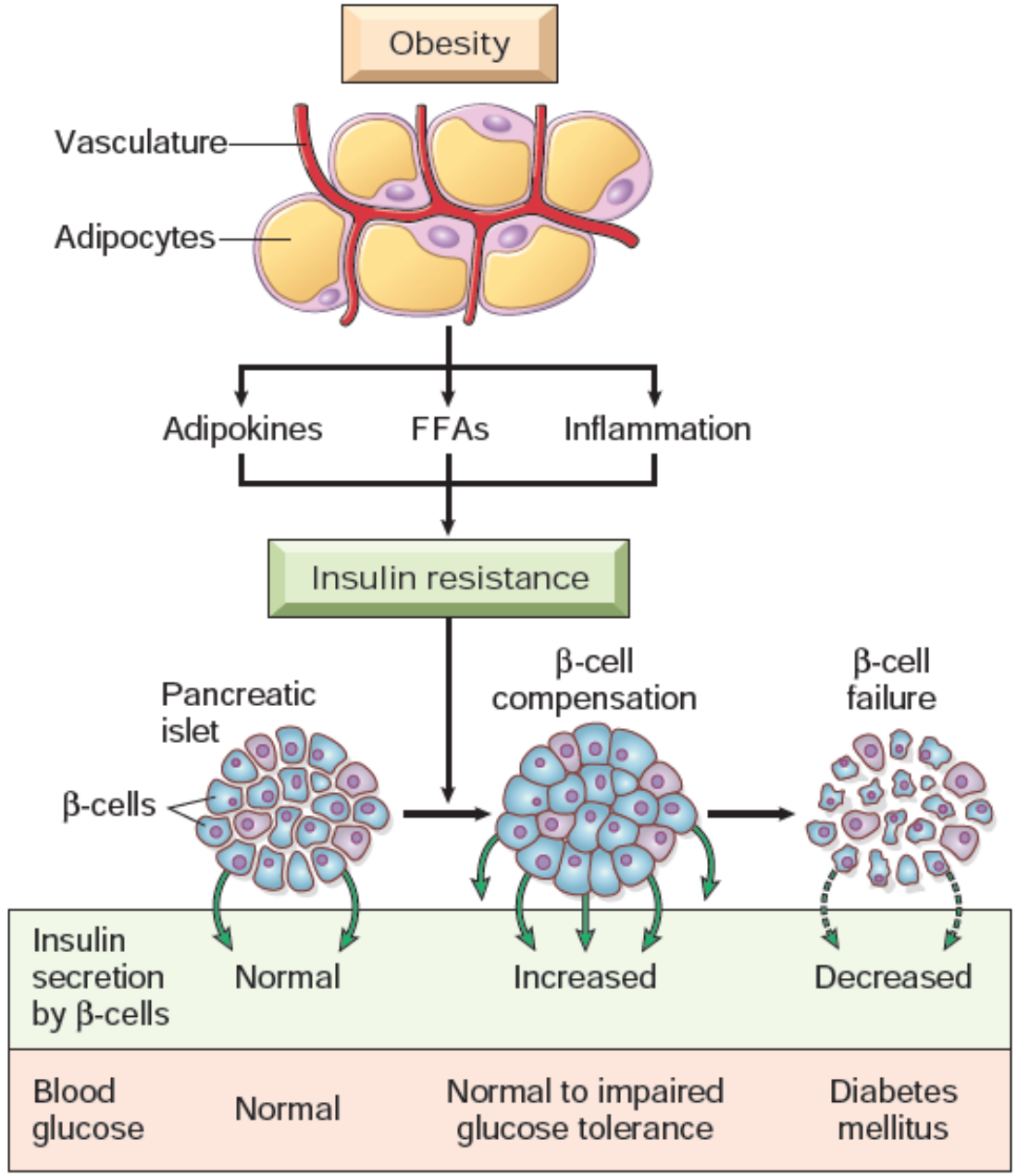
Several mechanisms have been implicated in promoting β-cell dysfunction in type 2 diabetes, including:

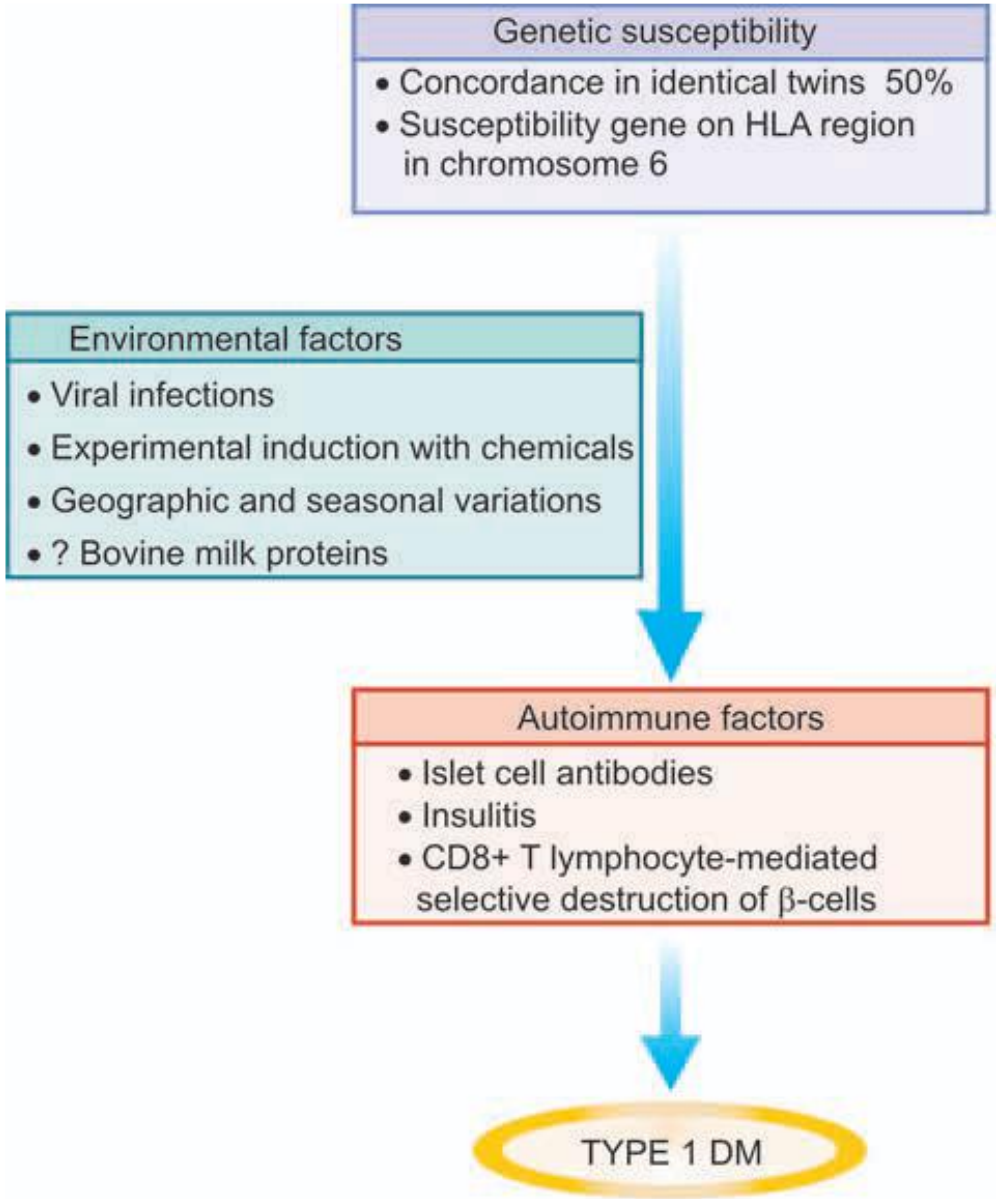
- Excess free fatty acids that compromise β cell function and attenuate insulin release (“lipotoxicity”)
- impact of chronic hyperglycemia (“glucotoxicity”)
- An abnormal “incretin effect,” leading to reduced secretion of GIP and GLP-1, hormones that promote insulin release


ENVIRONMENT
EXCESSIVE NUTRITION/OBESITY
Insulin Resistance
Increased Metabolic Load
Systemic Inflammation
GENETIC SUSCEPTIBILITY
ISLET RESPONSE
Inflammatory Stress
ER Stress
Metabolic/Oxidative Stress
Amyloid Stress
Stressed Islet Integrity
DECREASED β-CELL FUNCTION AND MASS
TYPE 2 DIABETES

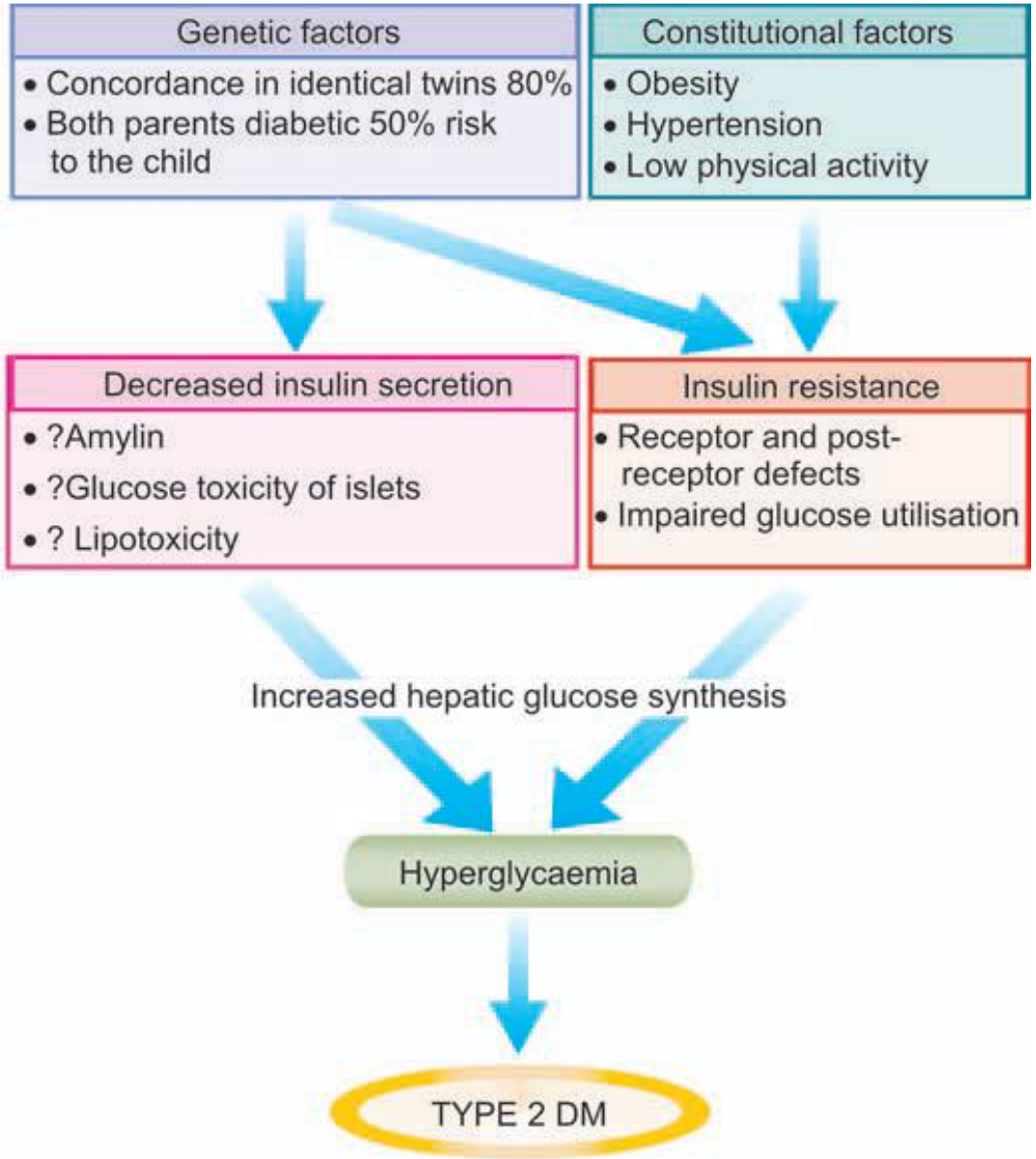
Pathophysiology of Type 2 DM



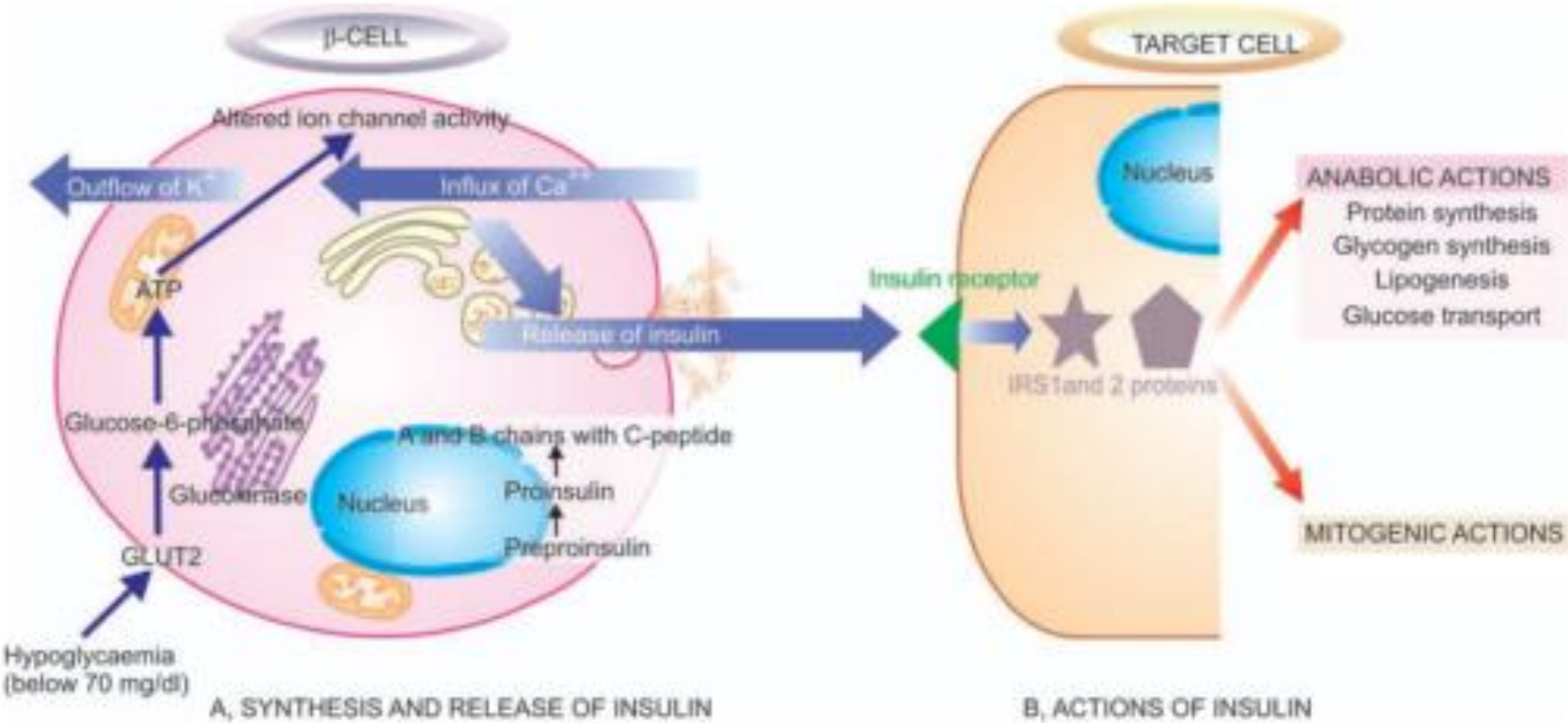

Obesity
Vasculature
Adipocytes
Adipokines
FFAs
Inflammation
Insulin resistance
Pancreatic islet
β-cells
β-cell compensation
β-cell failure
Insulin secretion by β-cells
Normal
Increased
Decreased
Blood glucose
Normal
Normal to impaired glucose tolerance
Diabetes mellitus



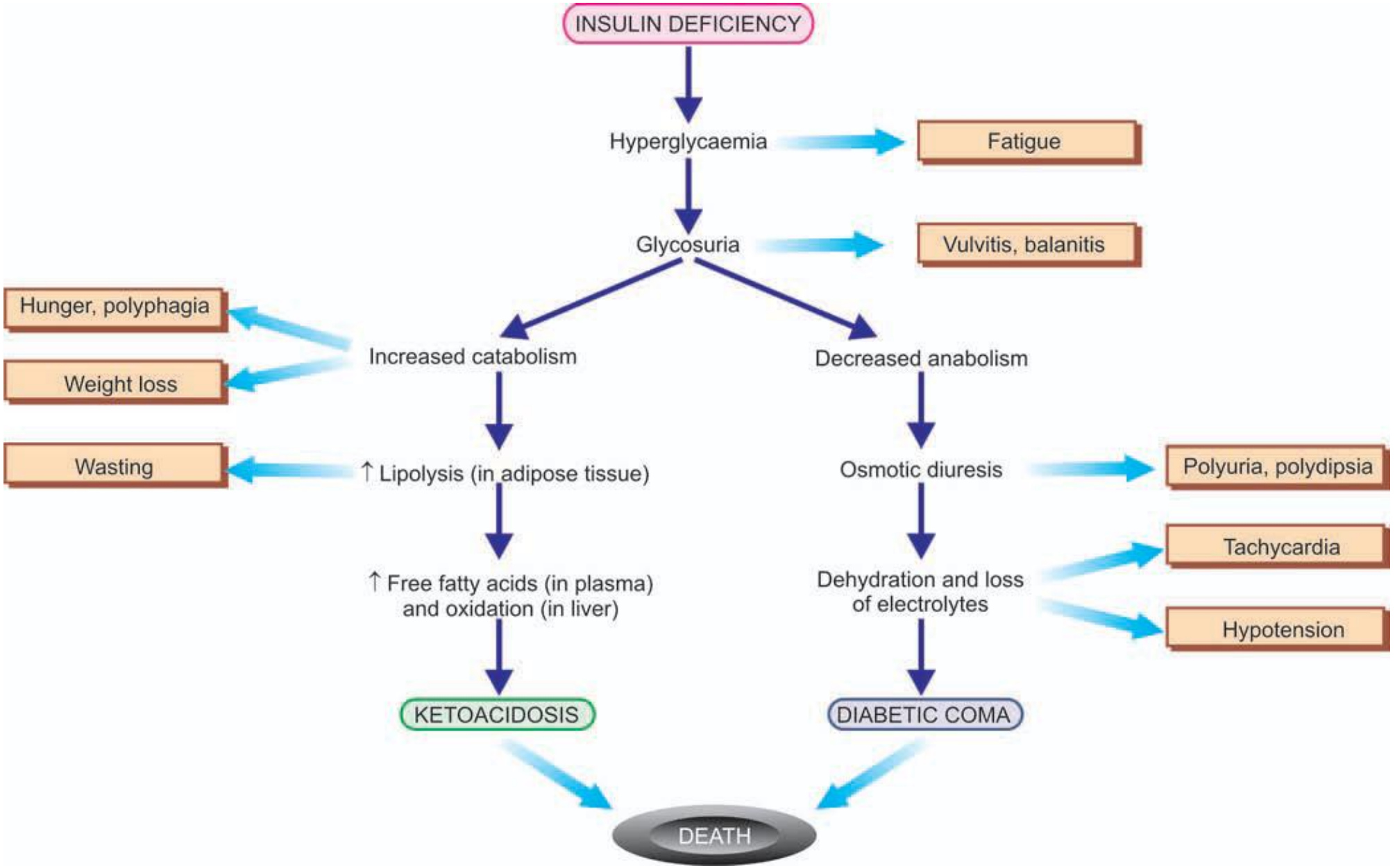
A, PATHOGENESIS OF TYPE 1 DIABETES MELLITUS



B, PATHOGENESIS OF TYPE 2 DIABETES MELLITUS


β-CELL
Altered ion channel activity
Outflow of K+
Influx of Ca++
ATP
Release of insulin
Glucose-6-phosphate
Glucokinase
GLUT2
Hypoglycaemia
(below 70 mg/dl)
A and B chains with C-peptide
Nucleus
Proinsulin
Preproinsulin
A, SYNTHESIS AND RELEASE OF INSULIN
TARGET CELL
Nucleus
Insulin receptor
IRS1and 2 proteins
ANABOLIC ACTIONS
Protein synthesis
Glycogen synthesis
Lipogenesis
Glucose transport
MITOGENIC ACTIONS
B, ACTIONS OF INSULIN

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



- Diabetic Macrovascular Disease-

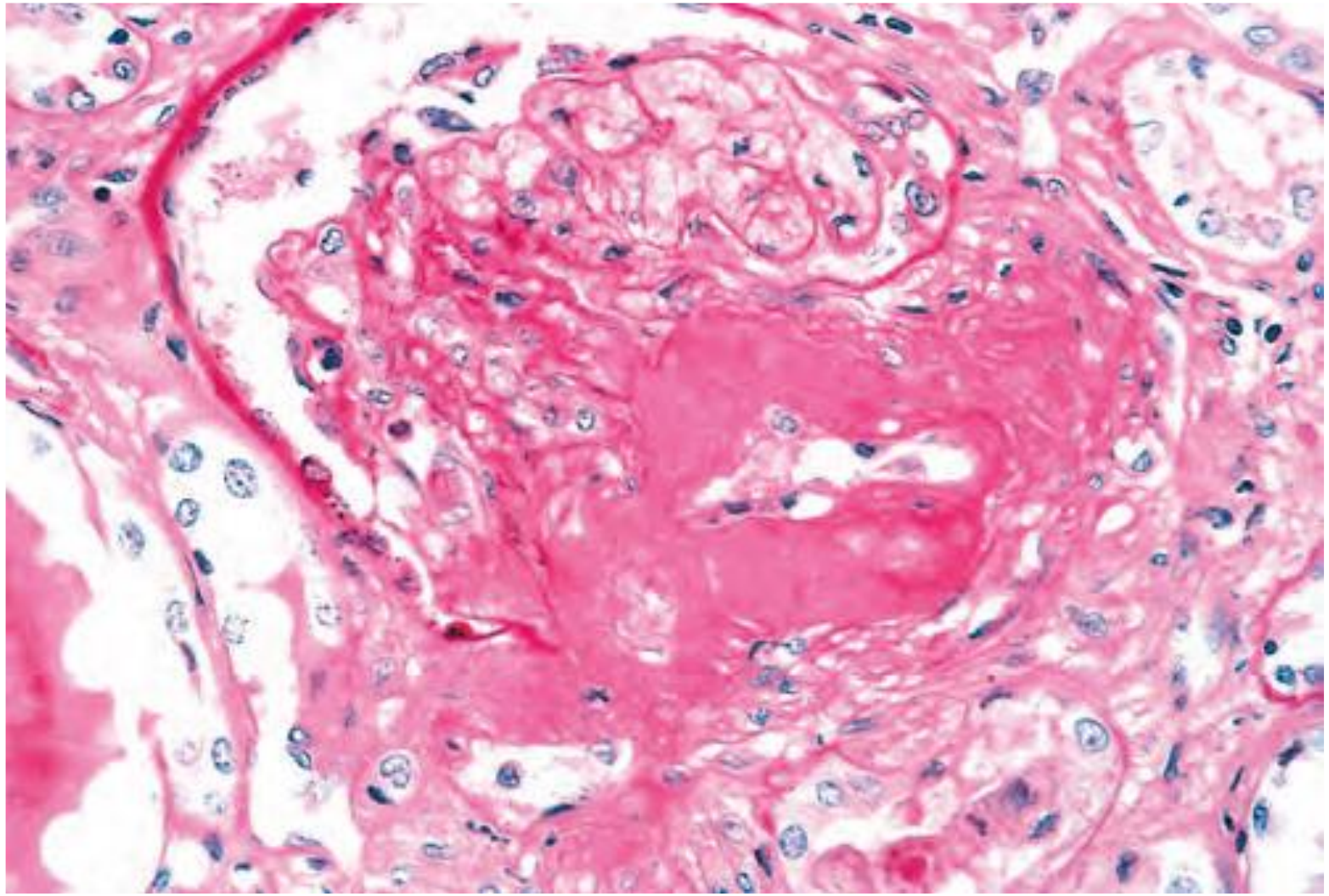
➢ hallmark of diabetic macrovascular disease is accelerated atherosclerosis involving the aorta and large- and medium-sized arteries

➢ Myocardial infarction

➢ Gangrene of the lower extremities

➢ Hyaline arteriolosclerosis

renal hyaline arteriolosclerosis



- Diabetic Nephropathy-

Three lesions are encountered:

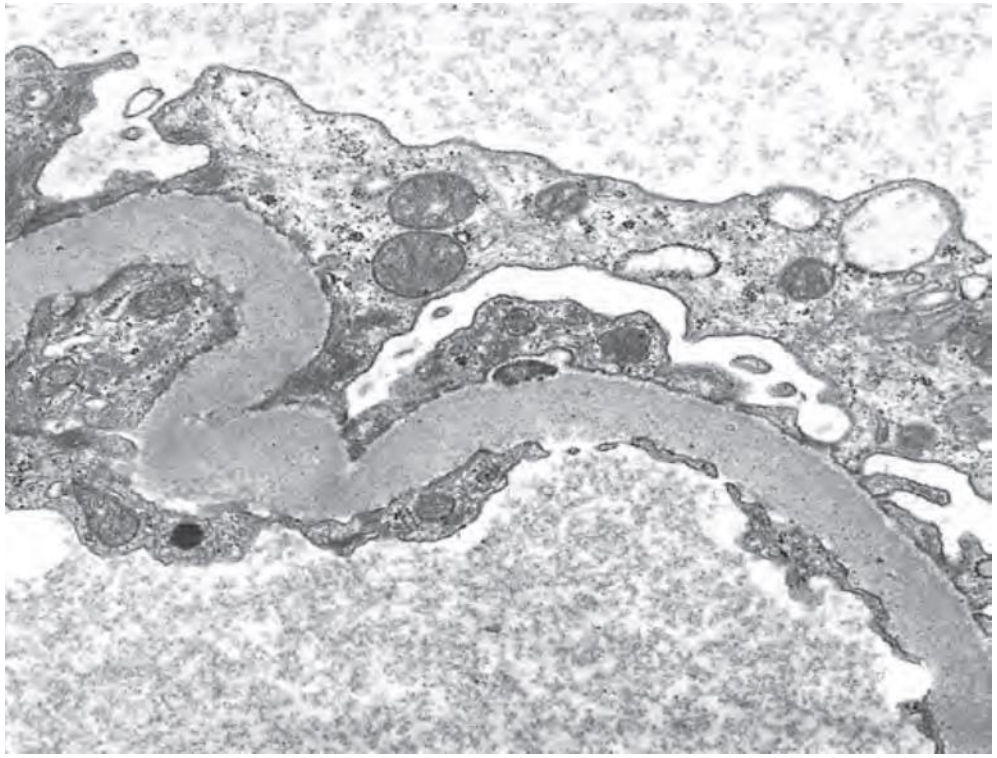
(1) glomerular lesions

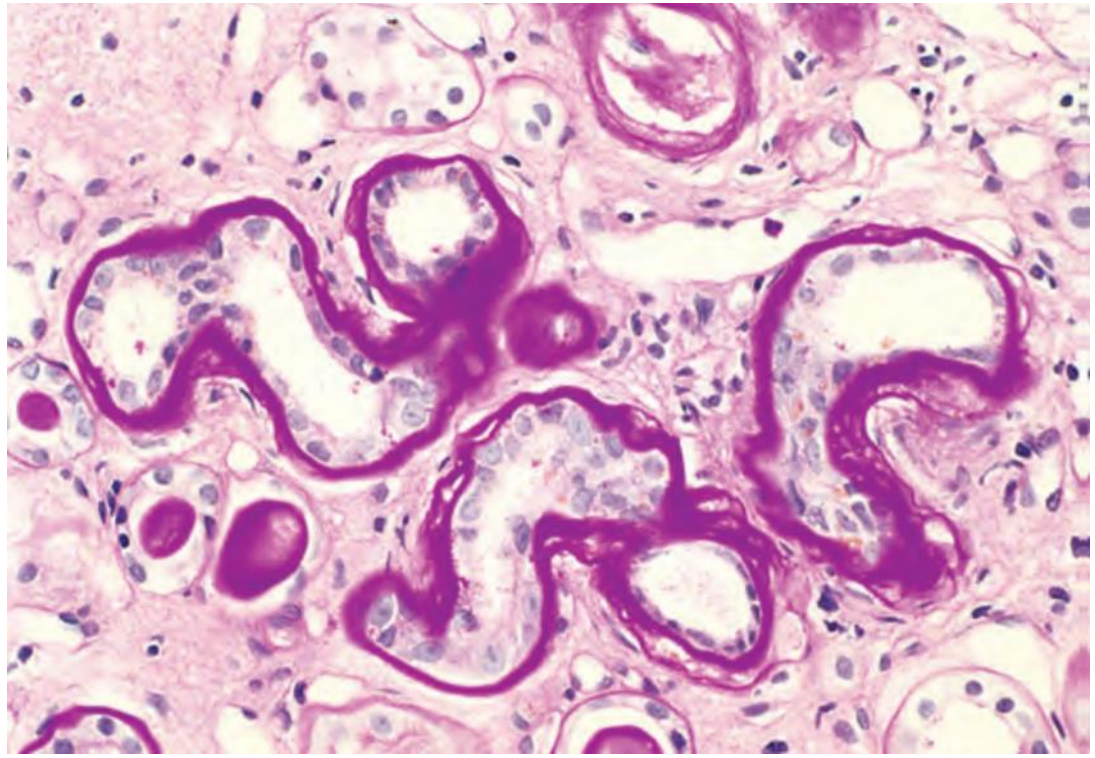
(2) renal vascular lesions

(3) pyelonephritis, including necrotizing papillitis

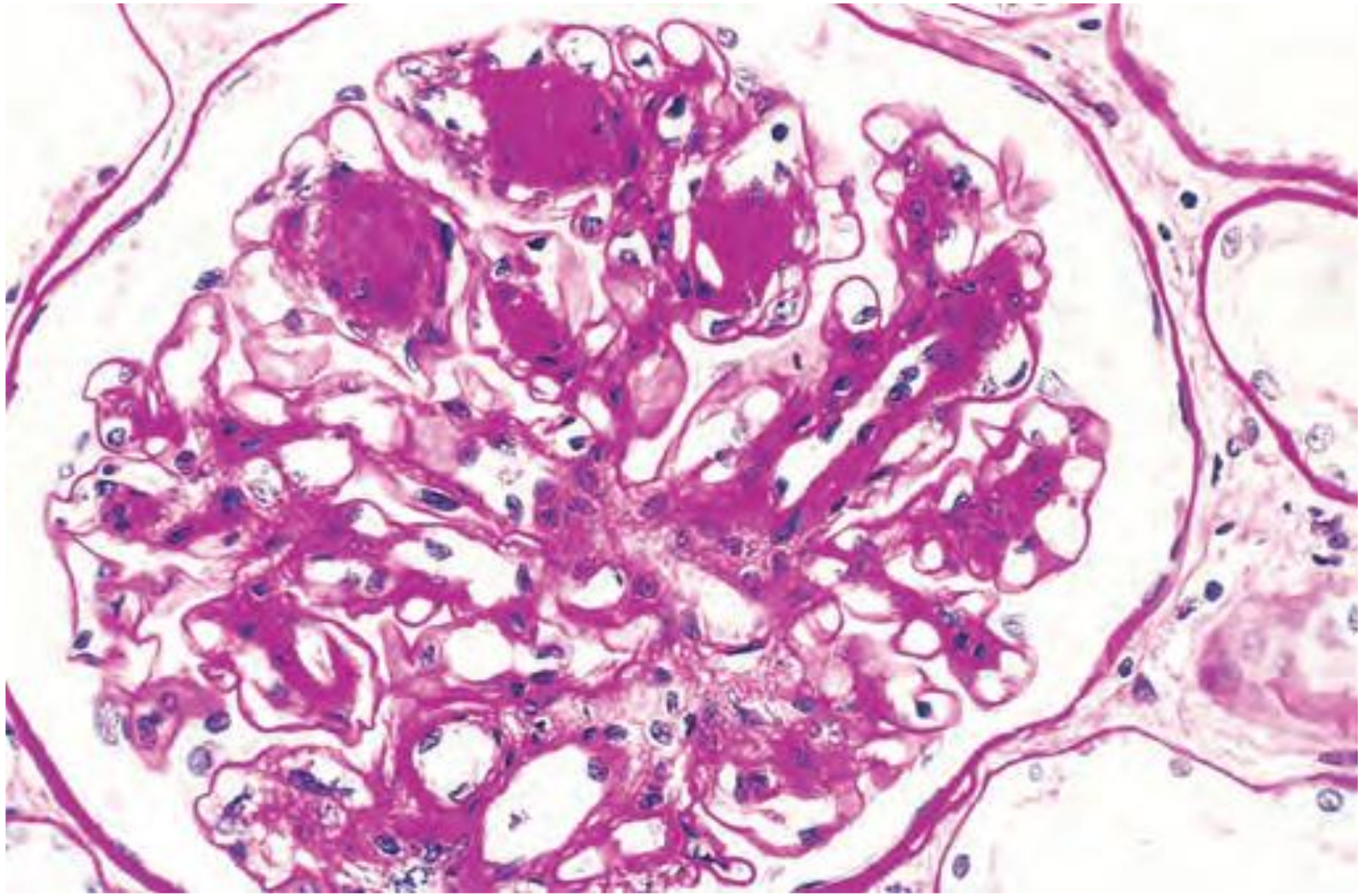
- Glomerular lesion-

➢Capillary Basement Membrane



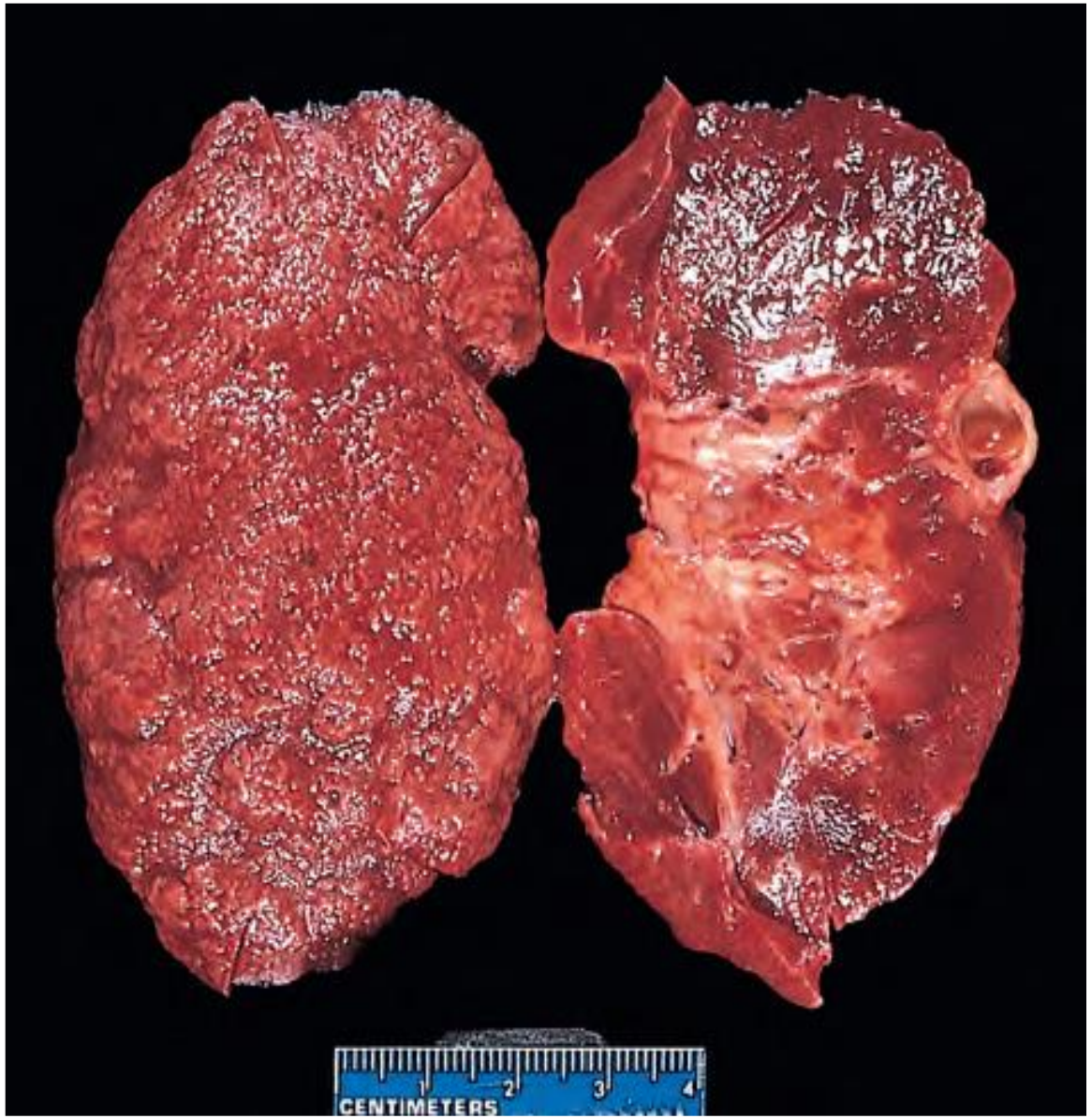


Diffuse and nodular diabetic glomerulosclerosis (PAS stain).



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

Nephrosclerosis

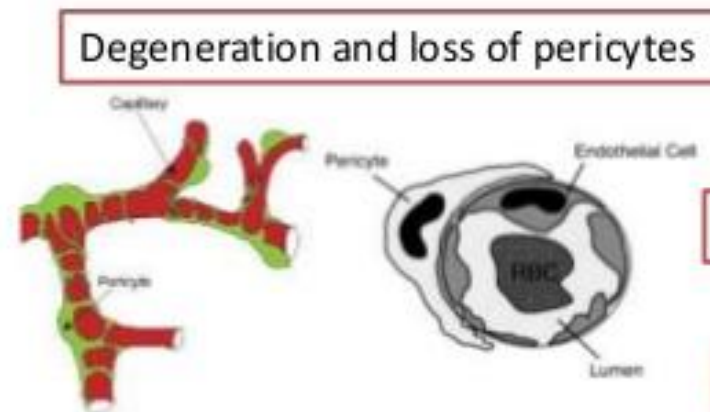


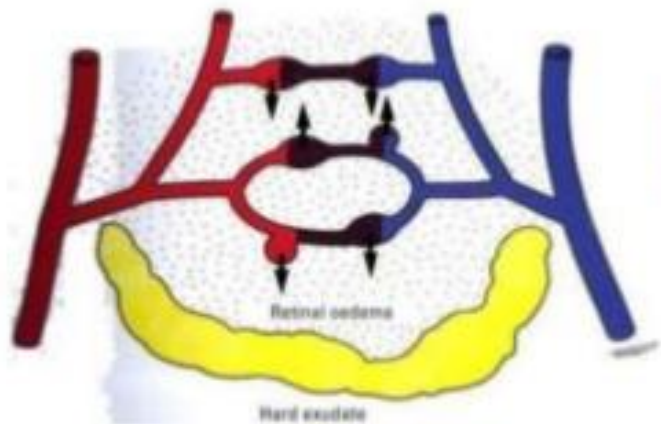
Diabetic Ocular Complications-

Histologically,

- Non proliferative (non-proliferative)
- proliferative retinopathy

Microvascular leakage

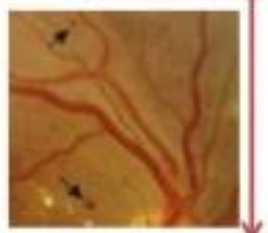




Degeneration and loss of pericytes → Capillary wall weakening

Capillary wall weakening → Plasma leakage → Retinal edema → Hard exudate (Circinate pattern)

Capillary wall weakening → microaneurysm → Intraretinal hemorrhage



Microvascular occlusion

Endothelial cell damage and proliferation

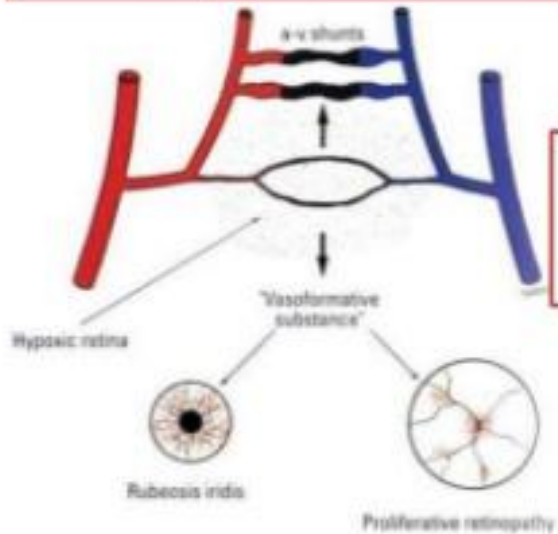
Capillary basement membrane thickening

Increased plasma viscosity
Deformation of RBC
Increased platelets stickiness

Decreased capillary blood flow and perfusion

Retinal hypoxia

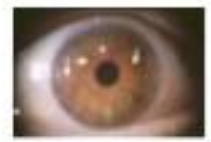
VEGF



A-V shunt
IRMA
Cotton wool spots

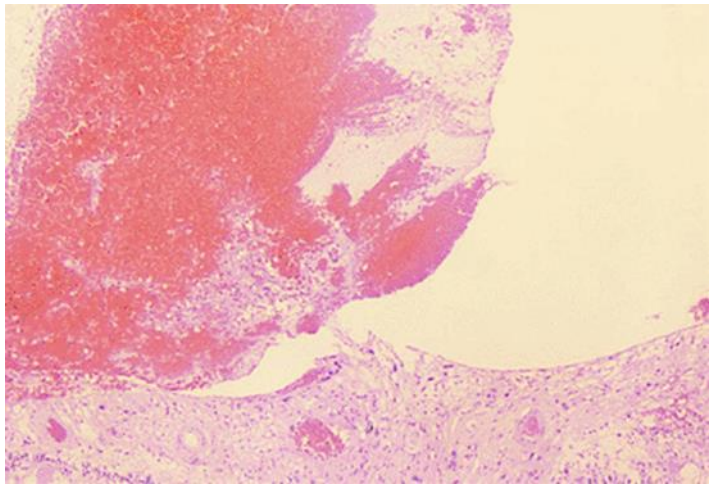
Neovascularization and fibrovascular proliferation

Rubeosis iridis



Proliferative retinopathy

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

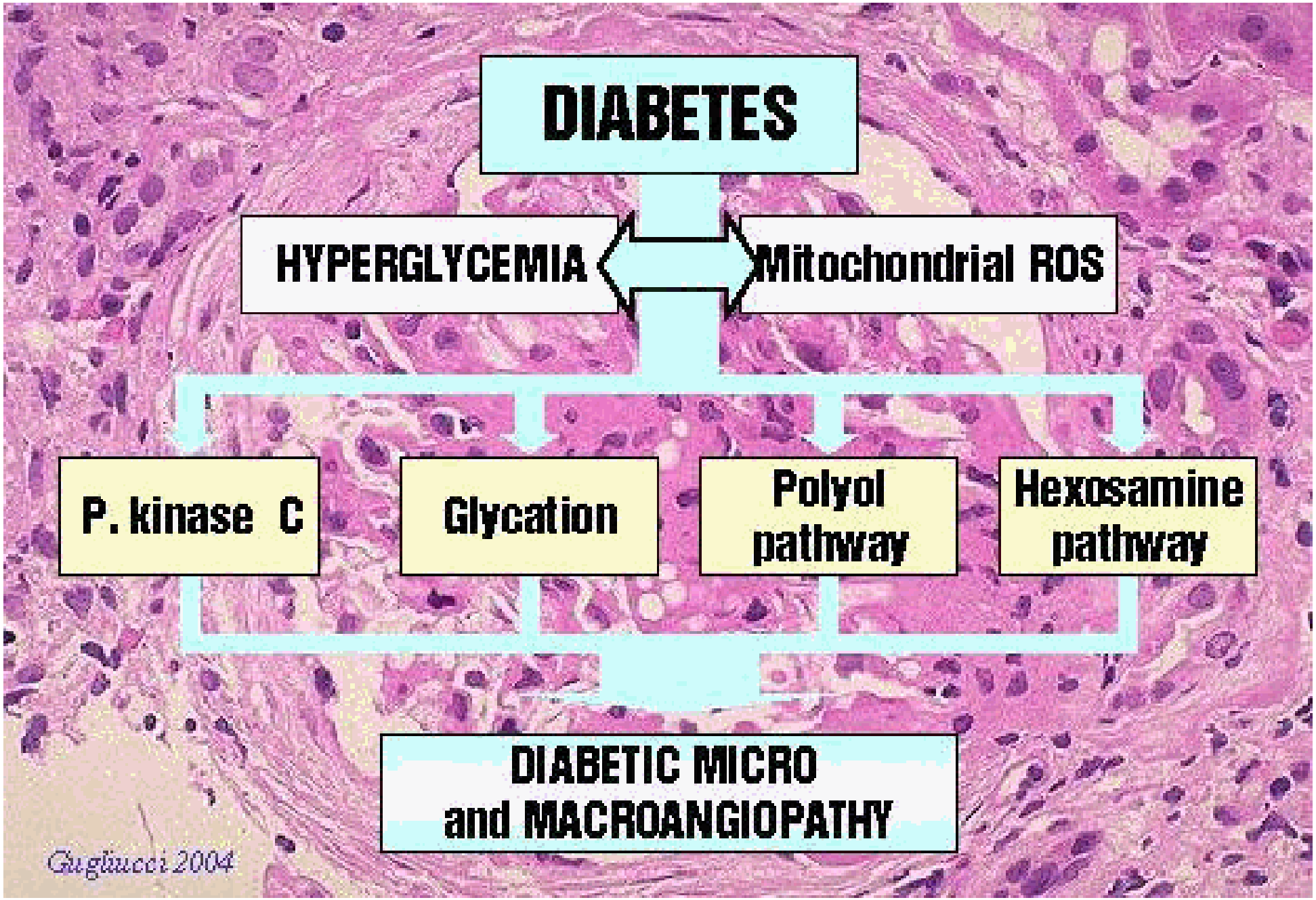


- iii) Proliferation of astrocytes and fibrous tissue around the new blood vessels.
- iv) Fibrovascular and gliotic tissue contracts to cause retinal detachment and blindness.

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


DIABETES
HYPERGLYCEMIA
Mitochondrial ROS
P. kinase C
Glycation
Polyol pathway
Hexosamine pathway
DIABETIC MICRO and MACROANGIOPATHY
Giugliucci 2004

Acute metabolic complications:

- diabetic ketoacidosis
- hyperosmolar nonketotic coma
- hypoglycaemia

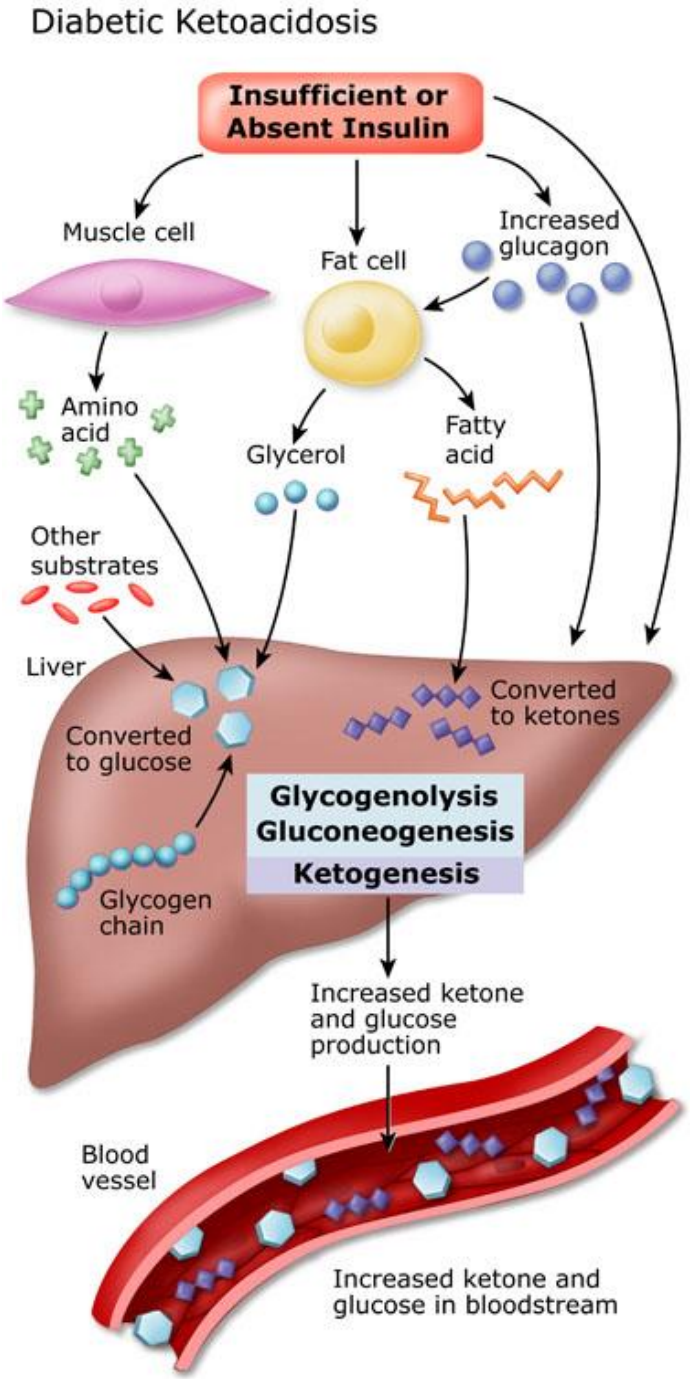
1.Diabetic ketoacidosis (DKA), complication of type 1 DM.

Lack of insulin

Lypolysis

Free fatty acid in plasma

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



MANAGEMENT OF DKA

Monitor **A**irway, **B**reathing and **C**irculation

Administer Intravenous Fluids

2-3 L of 0.9% NS over 1-3 hours

↓

Step down to 0.45% NS at 250-500 mL/hr

↓ when blood glucose level = 250 mg/dL

Add 5% Glucose to 0.45% NS at 150-250 mL/hr

Check serum K^+ level

- < 3.5 mEq/L → Give K^+ at 40-80 mEq/hr
- 3.5 to 5 mEq/L → Give K^+ at 10 mEq/hr

Administer Short-Acting/ Regular Insulin

0.1 units/kg i.v. bolus

↓

0.1 units/kg/hr i.v. infusion

↓ when blood glucose 150 - 250 mg/dL

0.05-0.1 units/kg/hr i.v. infusion

↓ When patient starts to eat

2-4 hr overlap in insulin infusion and long-acting insulin injection

2.Hyperosmolar hyperglycaemic nonketotic coma (HHS)-

High Blood sugar

↓

High plasma osmolality

↓

Hyperglycemic diuresis

↓

Dehydrartion

↓

CNS complication

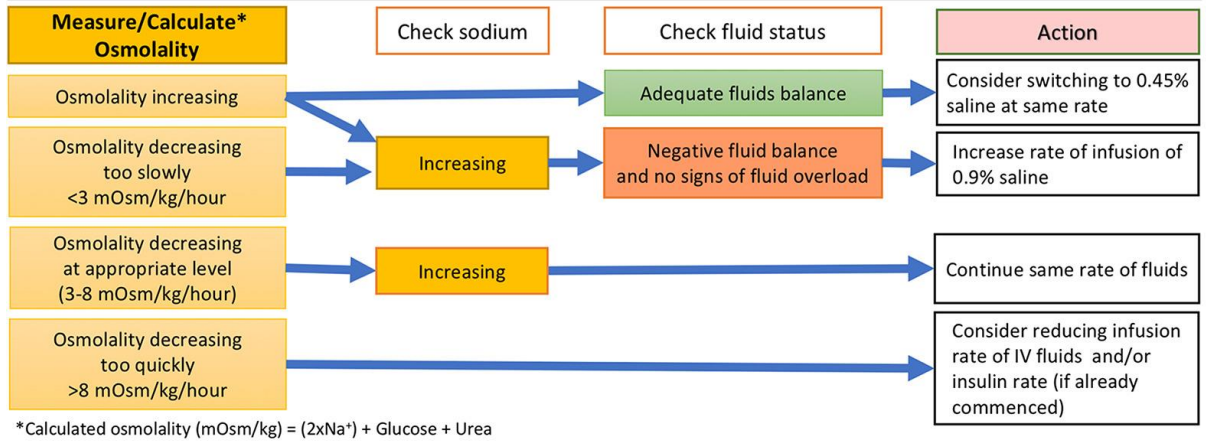
Table I. Comparison of HHS and DKA

	HHS	DKA
Hyperglycemia	+++	+ to +++
Ketosis/Acidosis	-/+	++ to +++
Dehydration	+++	+ to +++
Osmolality	+++ (> 330 mosm/Kg)	+ to +++
Electrolyte Deficits	+++	+ to +++

Hyperosmolar Hyperglycaemic State (HHS) care pathway in adults

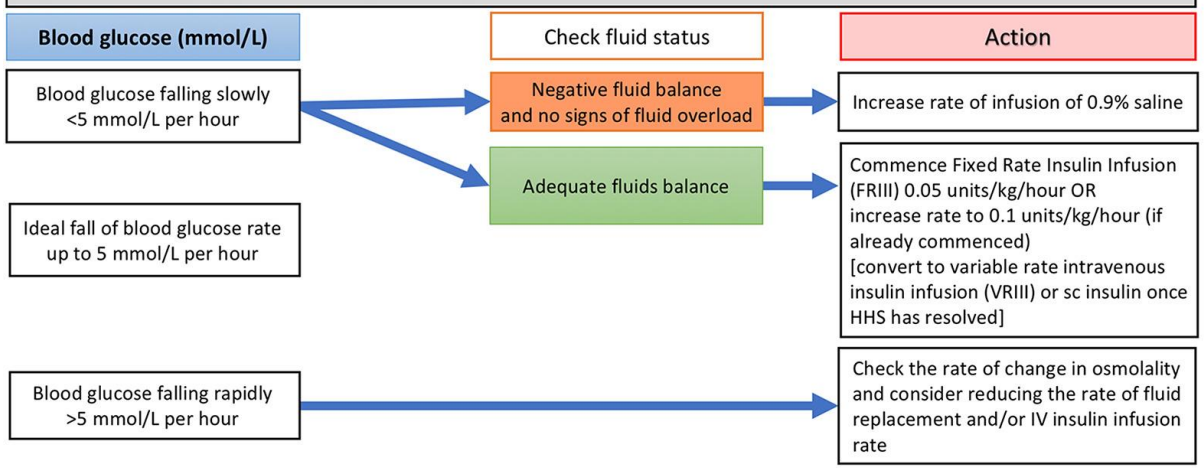
JBDS-IP Joint British Diabetes Societies for inpatient care

Figure 1: Managing osmolality changes during treatment of HHS



*Calculated osmolality (mOsm/kg) = (2xNa⁺) + Glucose + Urea

Figure 2: Managing glucose changes during treatment of HHS



If the parameters in Figures 1 and 2 above are not met, seek specialist input early to tailor the management according to the individual's needs

Table 1: Escalate to ICU/outreach if any of the following is present:

- Osmolality >350 mOsm/kg
- Sodium >160 mmol/L
- Venous/arterial pH <7.1
- Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (≥6 mmol/L) on admission
- Glasgow Coma Scale (GCS) <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
- Oxygen saturation <92% on air (assuming normal baseline respiratory function)
- Systolic blood pressure <90 mmHg
- Pulse >100 or <60 beats per minute
- Urine output <0.5 ml/kg/hour
- Serum creatinine >200 µmol/L and/or Acute kidney injury
- Hypothermia
- Macrovascular event such as myocardial infarction or stroke
- Other serious co-morbidity

Table 2: Potassium replacement guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in infusion solution
≥6.0	Senior review ICU/outreach
5.5-5.9	Nil
3.5-5.5	40 mmol/L
<3.5	Senior review. Additional potassium is required (via central line in high dependency unit).

@JBDSIP October 2022

3.Hypoglycaemia-

Ill or medicated individual
1. Drugs
    - Insulin or insulin secretagogue
    - Alcohol
    - Others (Table 2)
2. Critical illnesses
    - Hepatic, renal, or cardiac failure
    - Sepsis (including malaria)
    - Inanition
3. Hormone deficiency
    - Cortisol
    - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
4. Nonislet cell tumor

Seemingly well individual
5. Endogenous hyperinsulinism
    - Insulinoma
    - Functional β-cell disorders (nesidioblastosis)
        - Noninsulinoma pancreatogenous hypoglycemia
        - Post gastric bypass hypoglycemia
    - Insulin autoimmune hypoglycemia
        - Antibody to insulin
        - Antibody to insulin receptor
    - Insulin secretagogue
    - Other
6. Accidental, surreptitious, or malicious hypoglycemia

LATE SYSTEMIC COMPLICATIONS-

1. Atherosclerosis-

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

2.Diabetic microangiopathy

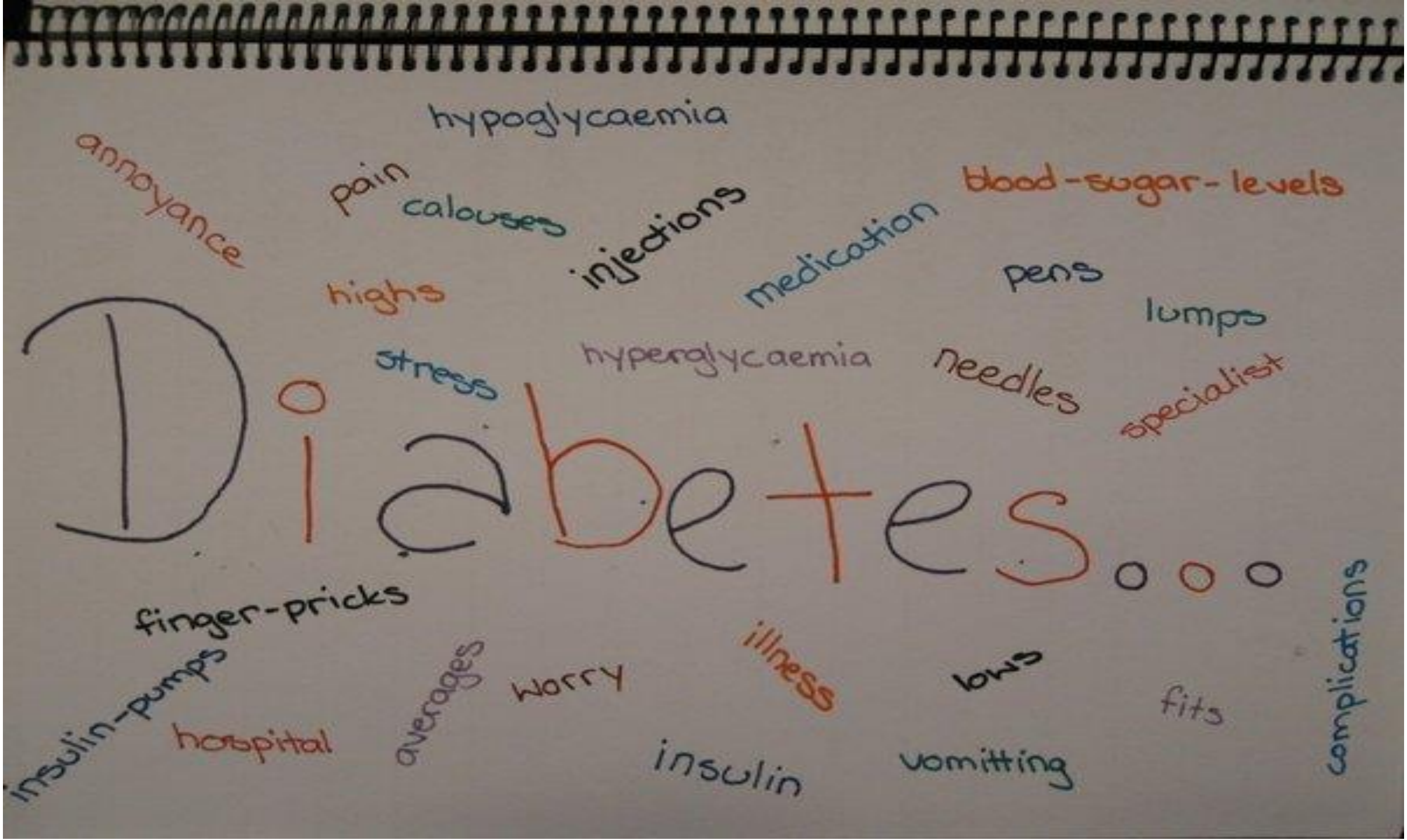
3. Diabetic nephropathy

4. Diabetic neuropathy

5. Diabetic retinopathy

6. Infections-

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


hypoglycaemia
annoyance
pain
calouses
injections
blood-sugar-levels
medication
pens
highs
lumps
stress
hyperglycaemia
needles
specialist
Diabetes...
finger-pricks
insulin-pumps
averages
worry
illness
lows
fits
complications
hospital
insulin
vomitting