PATHOPHYSIOLOGY OF CARBOHYDRATE METABOLISM

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A. Physiologic remarks:

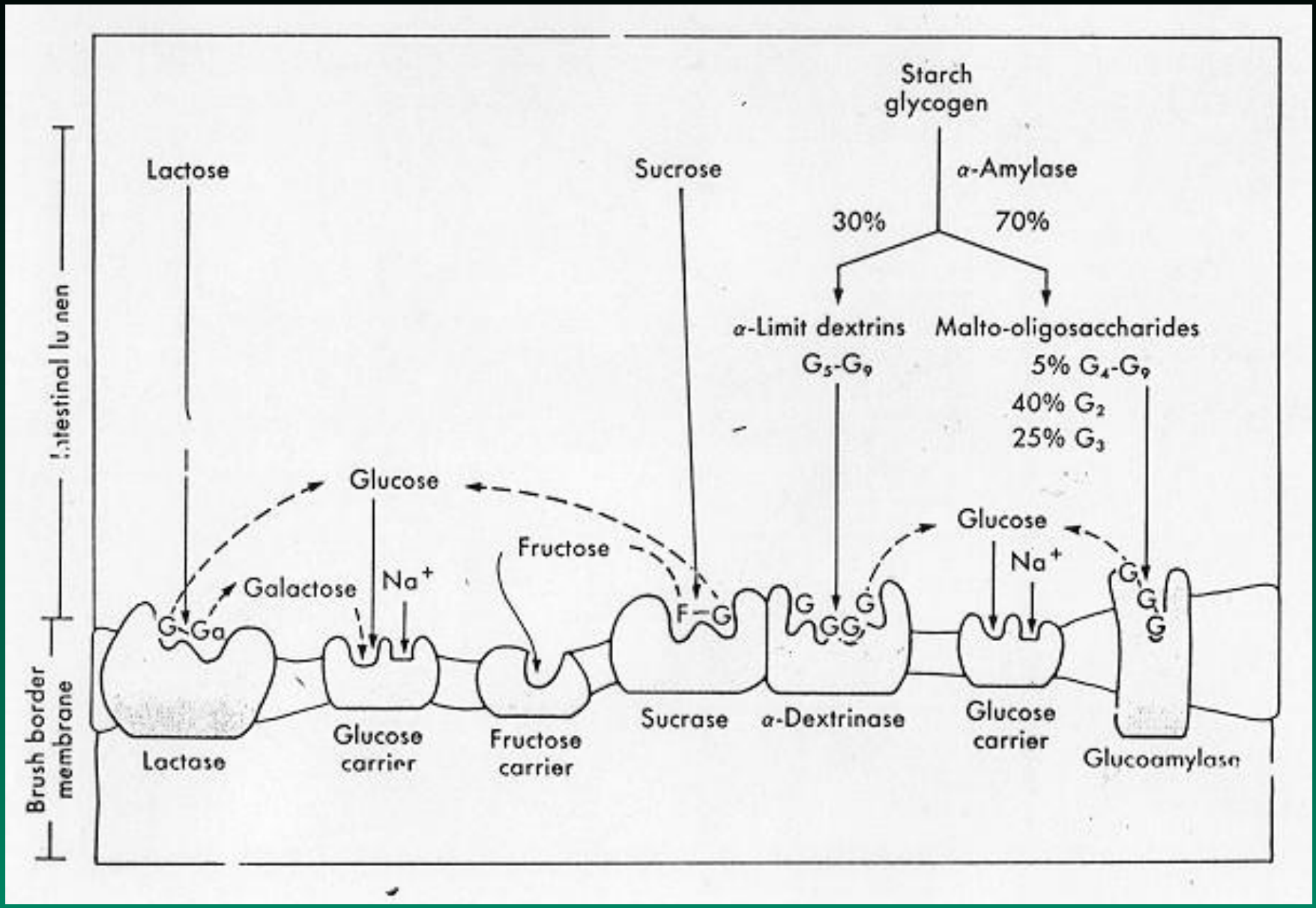
Carbohydrates are present in food in various forms:

1. *simple sugars* - monosaccharides

2. *complex chemical units* - disaccharides
- polysaccharides

Processing of carbohydrates in GIT

Ingested carbohydrates → cleaving proces→ →monosaccharides → absorbtion in stomach, duodenum and proximal jejunum


Starch
glycogen
α-Amylase
30%
70%
Lactose
Sucrose
α-Limit dextrins
G5-G9
Malto-oligosaccharides
5% G4-G9
40% G2
25% G3
Intestinal lumen
Glucose
Fructose
Galactose
Na+
Glucose
Na+
Brush border membrane
Lactase
Glucose carrier
Fructose carrier
Sucrase
α-Dextrinase
Glucose carrier
Glucoamylase

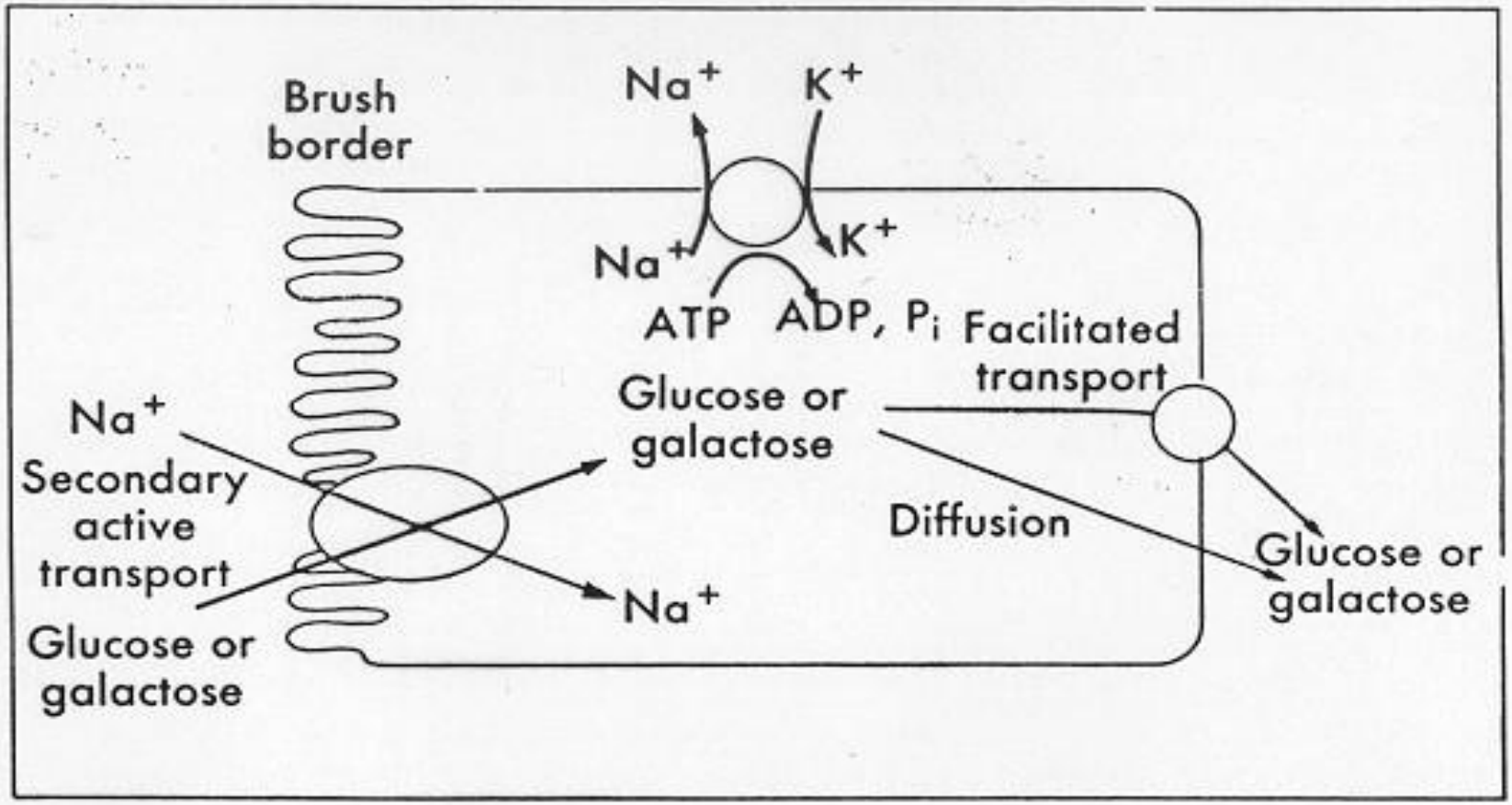


FIGURE 31-3 Major features of glucose and galactose absorption in the small intestine. Glucose and galactose enter the epithelial cell against a concentration gradient. The gradient of Na^+ provides the energy for sugar entry. Glucose and galactose leave the cell at the basolateral membrane by facilitated transport and by simple diffusion.

B. Disturbancies in Carbohydrate Resorbtion

1. Disaccharidase deficiency syndrome

saccharase = enzyme which hydrolyses disaccharide saccharose (to fructose and glucose)

laktase = enzyme which splits disaccharide lactose (to glucose and galactose)

maltase = enzyme which splits disaccharide maltose (to two molecule of glucose)

Pathomechanisms

a) Activity of disaccharidase is decreased → decreased hydrolysis of disaccharide → decreased resorbtion of substrate → increased concentration of disaccharide in small intestine lumen → increased osmotic activity of the lumen fluid → diarrhea

b) Activity of disaccharidase is decreased → increased concentration of disaccharide in small intestine lumen → →increased concentration of disaccharide in large intestine →

→ disaccharide fermentation by bacteria → increased concentration of lactic acid and fatty acids → →stimulation of intestine wall → abdominal cramps, bloating, diarrhea, acidic stools, explosive diarrhea

Lactase deficiency syndrome

Causes of lactase deficiency:

- genetic defect (primary)

- secondary to a wide variety of gastrointestinal diseases that damage the mucosa of the *small intestine (secondary)*

Disaccharide lactose is the principal carbohydrate **in milk**.

- Many persons showing milk intolerance prove to be lactase – deficient

- Primary lactase deficiency incidence is as high as 80 % to 90 % among African - Americans, Asians, and Bantus population

- Milk intolerance may not become clinically apparent until adolescence

Causes of secondary lactase deficiency:

- nontropical (celiac disease)and tropical sprue,
- regional enteritis,
- viral and bacterial infections of the intestinal tract,
- giardiasis, cystic fibrosis, ulcerative colitis,
- kwashiorkor, coeliac disease

Symptoms and signs - are mentioned at previous page

Monosaccharides malabsorbtion

Small intestine ability to resorb glucose and galactose is decreased

Cause: Specific transport system for galactose and glucose absorbtion in cells of small intestine is insufficient

Results: Symptoms and signs similar to disaccharidase deficiency syndrome

Glycogenosis (glycogen storage disease)

Autosomal recessive disease (inborn errors of metabolism, emzymopathy)

There are defects in degradation of glycogen.
The disturbances result in storage of abnormal glycogen,

or storage of abnormal amount of glycogen in various organs of the body
Example: Hepatorenal glycogenosis (Morbus von Gierke)

Cause: Deficit of glucose-6-fosfatase in liver and kidney
Results: Hypoglycemia in fasting individuals,

hyperlipemia, ketonemia

There are 9 other types of glycogenosis

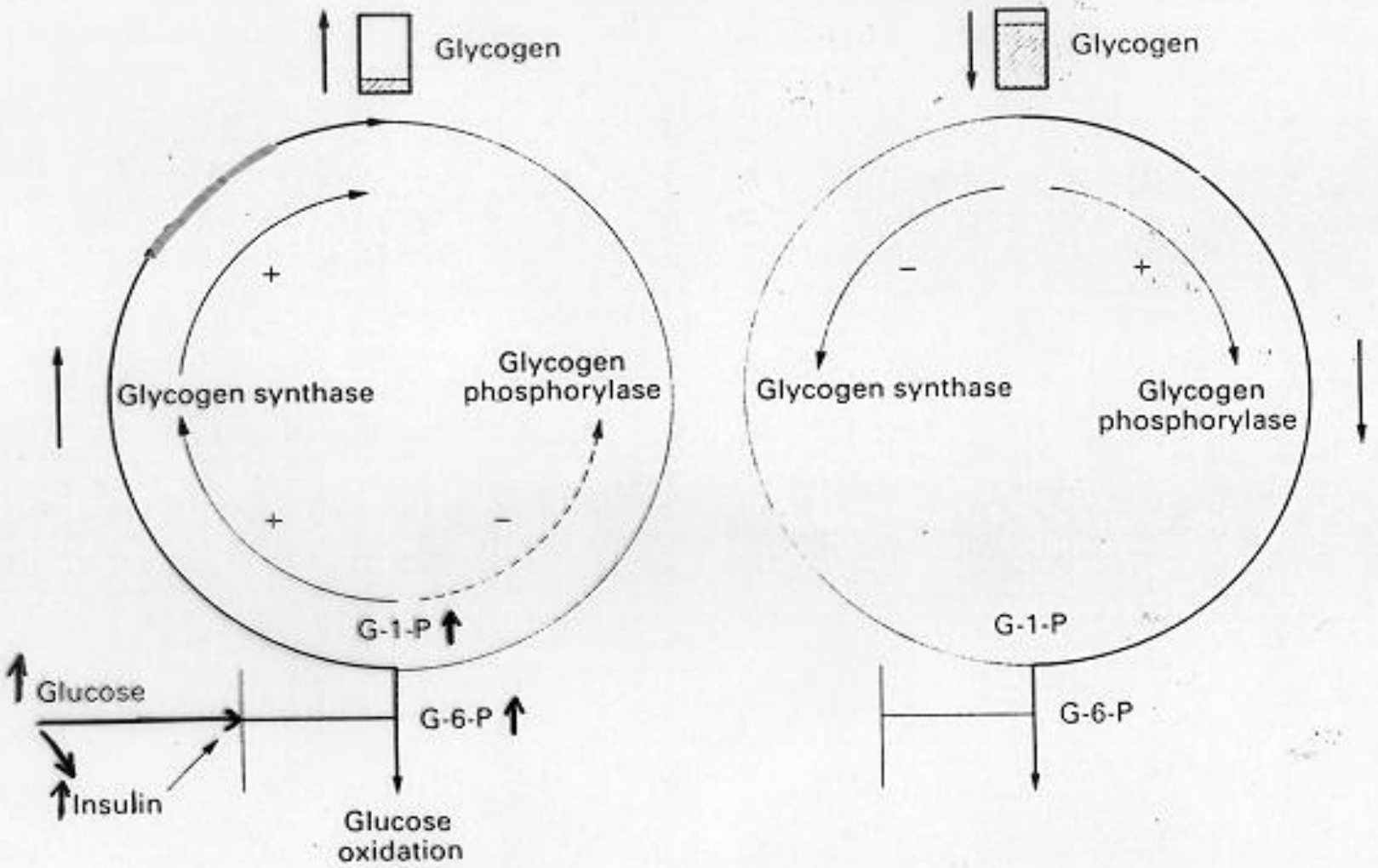


Figure 12 Physiological regulation of glycogen synthesis and breakdown. The rise in plasma glucose and insulin concentrations (see Figure 9) is followed by a rise in glucose-6-phosphate and glucose-1-phosphate which stimulates glycogen synthase activity and consequently glycogen synthesis while inhibiting glycogen phosphorylase activity (left). After the return of glycemia to basal levels (see Figure 9), the inhibition of glycogen phosphorylase activity by the increased concentration of glucose-6-phosphate is discontinued while, in contrast, the high intracellular glycogen concentration stimulates this enzymatic activity (right). This stimulates glycogen breakdown and the mobilization of glucose for oxidative purposes.

DIABETES MELLITUS

DIABETES MELLITUS

DM – complex chronic metabolic disorder leading to multiorgan complications

Main pathophysiological questions related to DM

- Why and how the DM develops?
- Why and how develop the complications of DM?
- What are the mechanisms involved in manifestation of diabetic symptoms and signs

Regulation of the blood glucose level depends on liver:

1. **extracting glucose from blood**
2. **synthesizing glycogen**
3. **performing glycogenolysis**
4. **performing gluconeogenesis**

To a lesser extent peripheral tissues (muscle and adipocytes) use glucose for their energy needs, thus contributing to maintinance of normal blood glucose level

The liver's uptake and output of glucose and the use of glucose by peripheral tissues depend on the physiologic balance of several hormones that:

1. **lower blood glucose level - insulin**
2. **rise blood glucose level - glucagon, epinephrine, GH, glucocorticoids...**

Definition of DM

DM is a chronic complex syndrome induced by **absolute** or **relative deficit of insuline** which is characterized by **metabolic disorders of carbohydrates, lipids and proteins.**

The metabolic disturbances are accompanied by **loss of carbohydrate tolerance, fasting hyperglycemia, ketoacidosis, decreased lipogenesis, increased lipolysis, increased proteolysis and some other metabolic disorders**

Classification of DM

(according to International Expert Committee, 1997)

Base for the classification are **etiopathogenetic mechanisms involved in onset and development of DM**

Types of DM

I. Diabetes mellitus - type 1: **due to destruction of beta cells of pancreatic islets**

Consequence: **absolute deficit of insulin**

A. subtype: **induced by autoimmunity processes**

B. subtype: **idiopathic mechanism**

II. Diabetes mellitus -type 2: at the beginning-**predominance of insulin resistance** and **relative deficit of insulin**(normo- or hyper -insulinemia), later on - **combination of impaired insulin secretion and simultaneous insulin resistance** (hypoinsulinemia, insulin resistance)

III. Other specific types of DM

- DM due to **genetic defects of beta cells** of pancreas islets and due to **genetic defect of insulin function**
- DM due to **diseases influencing exocrine functions of pancreas** – - secondary is damaged endocrine function, too.
- DM due to **endocrinopathies, drugs, chemicals, infections, metabolic and genetic disturbances**

IV. Gestational DM - **glucose intolerance which onsets for the first time during pregnancy**

Main differences between "old" and "new" classification of diabetes mellitus

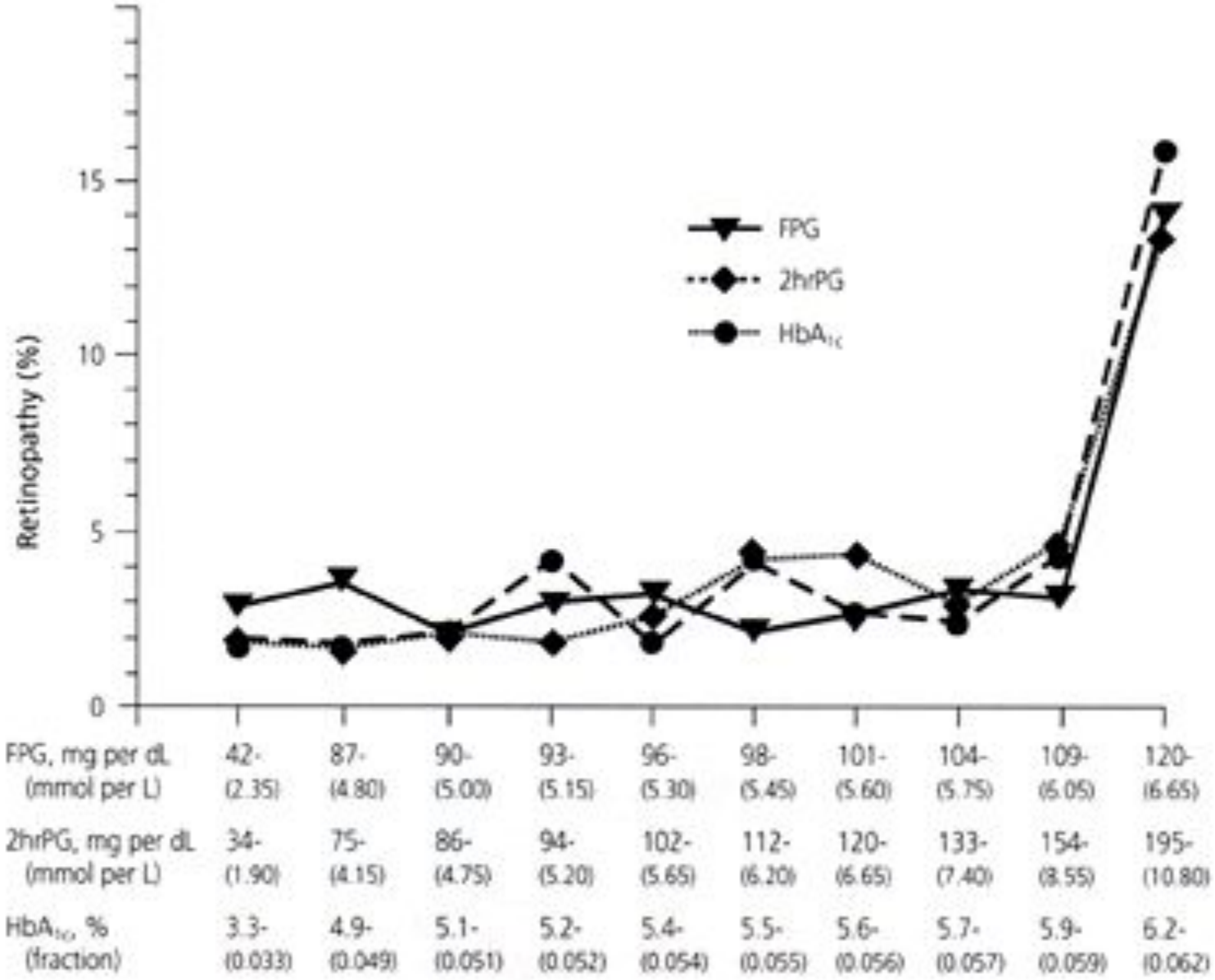
· In new classification of DM:

- terms IDDM and NIDDM are not used
- term DM due to malnutrition is not used
- terms - primary and secondary DM are not used

· New terms were introduced into new classification of DM:

* impaired fasting plasma glucose(FPG)
* impaired glucose tolerance(IGT)

Why?


Retinopathy (%)
0
5
10
15
FPG
2hrPG
HbA1c
FPG, mg per dL (mmol per L)
42- (2.35)
87- (4.80)
90- (5.00)
93- (5.15)
96- (5.30)
98- (5.45)
101- (5.60)
104- (5.75)
109- (6.05)
120- (6.65)
2hrPG, mg per dL (mmol per L)
34- (1.90)
75- (4.15)
86- (4.75)
94- (5.20)
102- (5.65)
112- (6.20)
120- (6.65)
133- (7.40)
154- (8.55)
195- (10.80)
HbA1c, % (fraction)
3.3- (0.033)
4.9- (0.049)
5.1- (0.051)
5.2- (0.052)
5.4- (0.054)
5.5- (0.055)
5.6- (0.056)
5.7- (0.057)
5.9- (0.059)
6.2- (0.062)

- **Normal fasting value of plasmatic glucose concentration: < 6.1 mmol/l**
- **Normal value of PGTT – blood glucose concentration 2 hs after beginning of test < 7.8 mmol/l**

- **New criteria for diagnose of DM**

1st: classic symptoms and signs of DM are present (polyuria, polydipsia, weight loss), **and increased day-time blood glucose concentration to 11.1 mmol/l and more**

or

2nd: fasting glucose level is 7.0 mmol/l and more

or

3rd: 2 hours glucose level in PGTT is 11.1 mmol/l and more

For confirmation of diagnosis DM positivity each of the mentioned parameters have to be confirmed next day by positivity any of the mentioned parameter

· **Impaired fasting plasma glucose:**
≥ 6.1 but < 7.0 mmol/l

· **Impaired glucose tolerance (IGT):**
Glucose tolerance test shows abnormal values but these

patients are asymptomatic and they do not meet the criteria for diagnosis of DM.

IGT criteria:

- fasting plasma glucose level can be normal
- 2 hours after intake glucose is plasma glucose level higher than normal (from 7.8mmol/l to 11.1mmol/l)

The individuals with IGT **are recognized as being at higher risk than the general population for the development of DM (about 1.5 - 4.0 % of patients with IGT → DM).**

Syndrome X (metabolic X syndrome)

- frequently occurs in people suffering form **visceral obesity**

Characteristic features:

- **insuline resistance**
- **compensatory hyperinsulinemia**
- **visceral obesity**
- **dyslipidemia (↑ LDL, ↑ TG, ↓ HDL)**
- **systemic hypertension**

Increased probability of DM-type2 development

Insuline Resistance (IR)

IR is one of the mechanisms involved in pathogenesis of IGT and DM, especially in DM type 2

Causes of insuline resistance:

1. **autoimmune reactions**
   - **development of anti-insulin antibodies**
   - **development of anti-insulin receptor antibodies**

2. **defects in the insulin receptor at the cell surface**
   a) **defect in receptor processing**
   b) **decrease in receptor number**

3. defective signal transduction
(from the receptor to the plasma of cell)

4. postreceptor defect

5. increased concentration of anti-insulinic hormones

Etiopathogenesis of DM

Type 1 DM - characteristics

- it is most typical in individuals **under 30 years** of age (juvenile DM)

- **80 % - 90 % of beta cells in the islets of Langerhans are destroyed**

Possible mechanisms of beta cells destruction:

a) by islet cell antibodies of the IgG class

b) by non-immune mechanism (idiopathic up to now)

Evidence suggest that type 1 DM is caused by a gradual process of autoimmune destruction of beta cells in genetically susceptive individuals

The result of beta cells destruction:

- **almost no or absolute no functional insulin is produced**
- **glucagon is present in relative excess**
- **individuals are prone to ketoacidosis**
- **insulin resistance is rare**
- **patients are insulin dependent**

Type 2 DM - characteristics

1. Primary disturbance:
- ↓ biological activity of insuline

2. Compensatory hyperinsulinemia
- due to ↑concentration of blood glucose

3. Insulinoresistentia:
- ↓ ability of insuline to inhibit production of glucose in liver → ↑glucose production

Type 2 DM -characteristics

- is rare in populations not affected by urban modernization
- adult onset (mostly after 40 years of age, slow, insidious onset)
- results from the action of several abnormal genes ; - inherited susceptibility, familial tendency stronger than for type 1 DM
- associated with long - duration obesity (mainly visceral)
- islet of Langerhans cells antibodies are rare
- increased insulin resistance
- nonspecific changes (damage) of islet cells
- usually not insulin dependent
- individuals are not ketosis prone (but they may form keton bodies under stress)

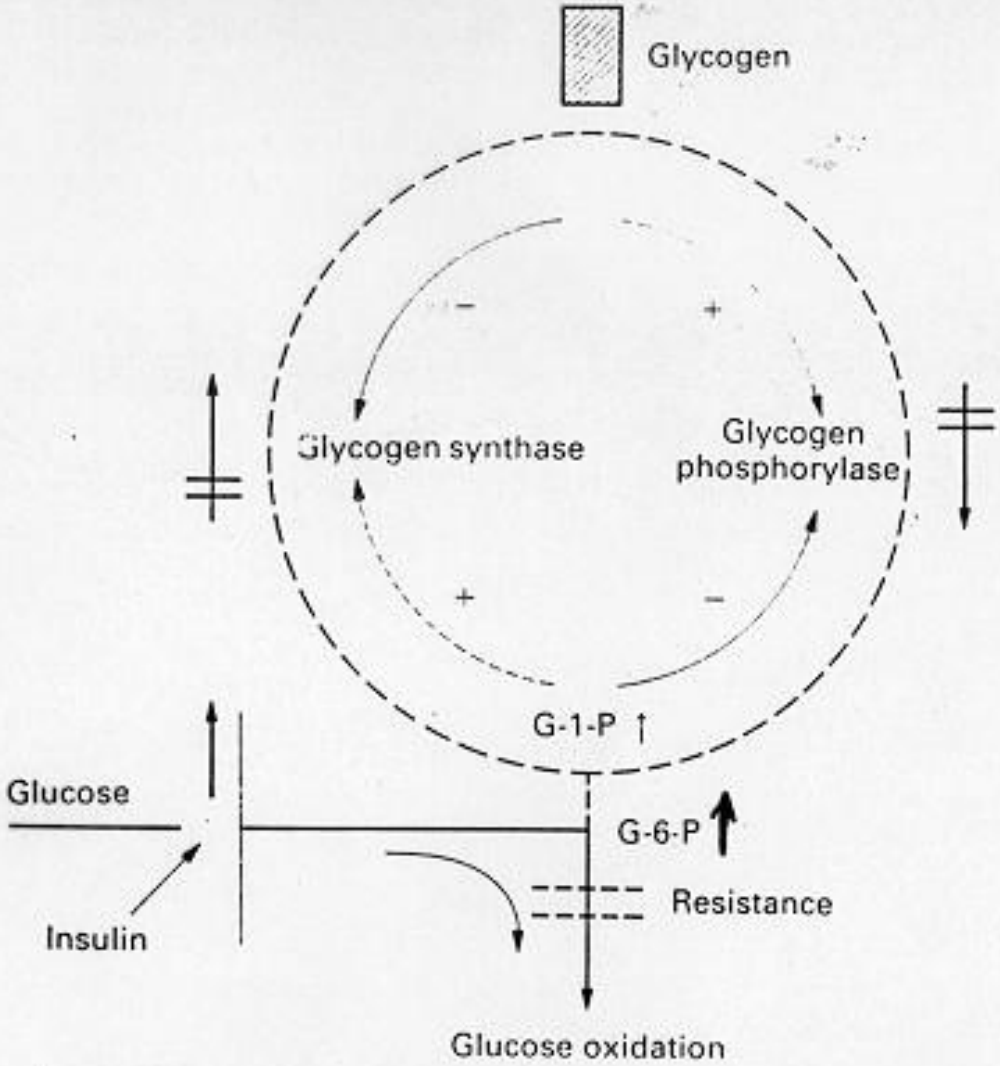


Figure 13 Inhibition of the function of the glycogen cycle in NIDDM. The absence of return of glycemia to basal levels (see Figure 9) prevents the breakdown of glycogen for oxidative purposes. The high glucose-6-phosphate and glucose-1-phosphate concentrations cause the inhibition of glycogen phosphorylase activity while the high glycogen concentrations resulting from the absence of glycogen breakdown inhibit glycogen synthase activity and consequently further glycogen synthesis. As a consequence of the important reduction in the activity of the glycogen cycle glucose oxidation originates essentially from exogenous glucose, i.e. from the high circulating glucose concentrations.

Main symptomes and signs of DM and mechanisms of their onset

Hyperglycemia:

- relative or absolute deficiency of insulin effect → ↓ transport of glucose to muscle and fat cells →↑ glycemia
- ↓ insulin effect →↑ gluconeogenesis in liver →↑ blood level of glucose
- ↑ glycogenolysis (?)

Glycosuria: hyperglycemia (8-15 mmol/l) → glycosuria

Polyuria: high blood level of glucose → increased amount of glucose filtered by the glomeruli of the kidney →absorbtion capacity of renal tubules for glucose is exceeded →glycosuria results, accompanied by large amounts of water lost in the urine (osmotic effect of glucose)

Polydipsia : high blood level of glucose → hyperosmolality of plasma →water moves from cells to ECF (IVF) → → intracellular dehydratation → → creation of thirst feeling (in hypothalamus) → → ↑intake of fluids

Polyphagia: depletion of cellular stores of carbohydrates, fats, and proteins results in cellular starvation and a corresponding increase in hunger

Weight loss : fluid loss in osmotic diuresis, loss of body tissue as fats and proteins are used for energy creation

Fatigue : metabolic changes result in poor use of food products → lethargy and fatique

Complications of Diabetes Mellitus

A. Acute complications

- Hypoglycemia
- Ketoacidosis
- Hyperosmolar hyperglycemic nonketotic coma

B. Chronic complications

- Diabetic micro- and macrovascular changes
- Diabetic neuropathy
- Diabetic retinopathy
- Diabetic nephropathy
- Other complications

A. Acute complications

1. Hypoglycemia (**< 3.3mmol/l of blood glucose**) - results from:

a) exogenous causes - overdose of insuline plus inadequate food intake, increased exercise
- overdose of oral hypoglycemic agents
- alcohol
- other agents (e.g. salicylates)

b) endogenous causes - insulinoma (neoplasm of beta cells of islet of Langerhans)
- extrapancreatic neoplasm (hepatomas, tumor of GIT)
- inborn errors of metabolism (fructose intolerance)

Symptoms and signs of hypoglycemia are caused by epinephrine release (sweating, shakiness, headache, palpitation) and by lack of glucose in the brain (bizarre behaviour, dullness, coma).

Hypoglycemia unawareness (HU)

Cause: antihypoglycemic mechanisms are insufficient

Result: hypoglycemia develops without warning symptoms and signs

Pathomechanism involved in HU development:

- Primary defect is localised to the CNS
  - ↓ or loss of neurotransmiter production on hypoglycemic stimulus
  - ↓ reactivity of peripheral tissues counterregulatory hormones

Consequences: Deep hypoglycemia → hypoglycemic coma → → death

2. Diabetic ketoacidosis - the most serious metabolic complication of DM

– It develops when there is **severe insulin insufficiency**

– Insulin insufficiency triggers a **complex metabolic reactions** which involve:

- decreased glucose utilisation → hyperglycemia and glycosuria

- acceleration of gluconeogenesis → hyperglycemia

- decreased lipogenesis and increased lipolysis→ increase oxidation of free fatty acids → **production of ketone bodies** (aceto-acetate, hydroxy-butyrate, and acetone) → **hyperketonemia** → **metabolic acidosis** → **coma**

3. Hyperosmolar hyperglycemic nonketotic coma(HHNC)
(hyperosmolar hyperglycemic syndrome)

a) - insulin is present to some degree → it inhibits fat breakdown → lack of ketosis

b) - insulin is present to some degree → its effectivity is less than needed for effective glucose transport → hyperglycemia → glycosuria and polyuria → body fluids depletion → intracellular dehydration → neurologic disturbancies (stupor, coma)

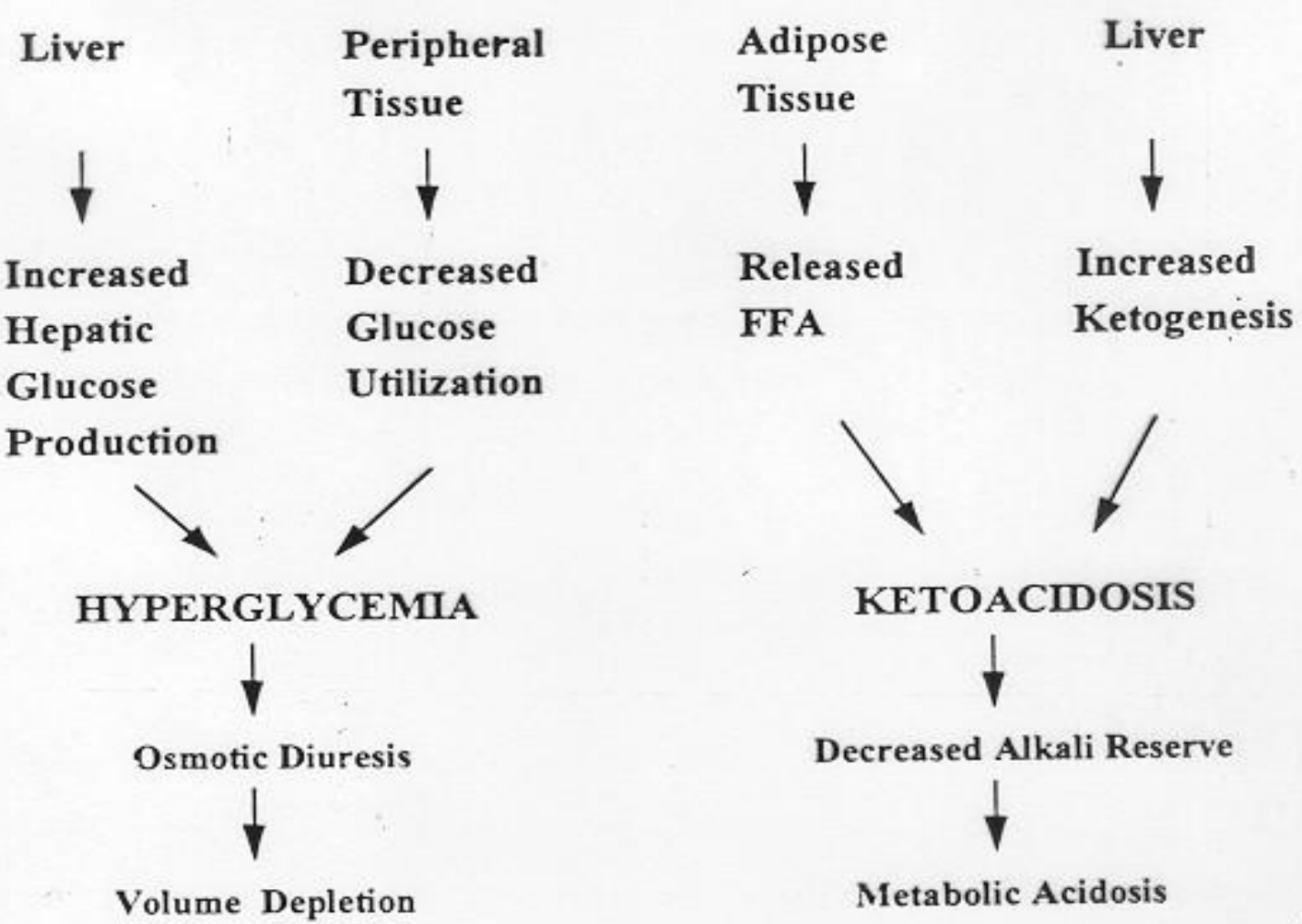


Figure 1. Pathogenesis of acute metabolic decompensation in diabetes mellitus. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHNS) are characterized by insulinopenia and increased counterregulatory hormones (glucagon, catecholamines, and cortisol). In general, two mechanisms account for the absence of ketoacidosis in HHNS, and include a higher level of pancreatic insulin reserve and lower levels of counterregulatory hormones in patients with HHNS compared with patients with DKA.

B. Chronic complications

Today, long-term survival of patient suffering from DM is the rule. As a result, the problems of neuropathy, microvascular disease, and macrovascular disease have become important

1. Diabetic neuropathies(DN) - probably the most common complication in DM

Pathogenesis:

a) vascular damage of vasa nervorum

b) metabolic damage of nerve cels

c) non-enzymatic glycation of proteins

The very first morphologic and functional changes:
- axonal degeneration preferentially involved unmyelinated fibers

(in spinal cord, the posterior root ganglia, peripheral nerves)

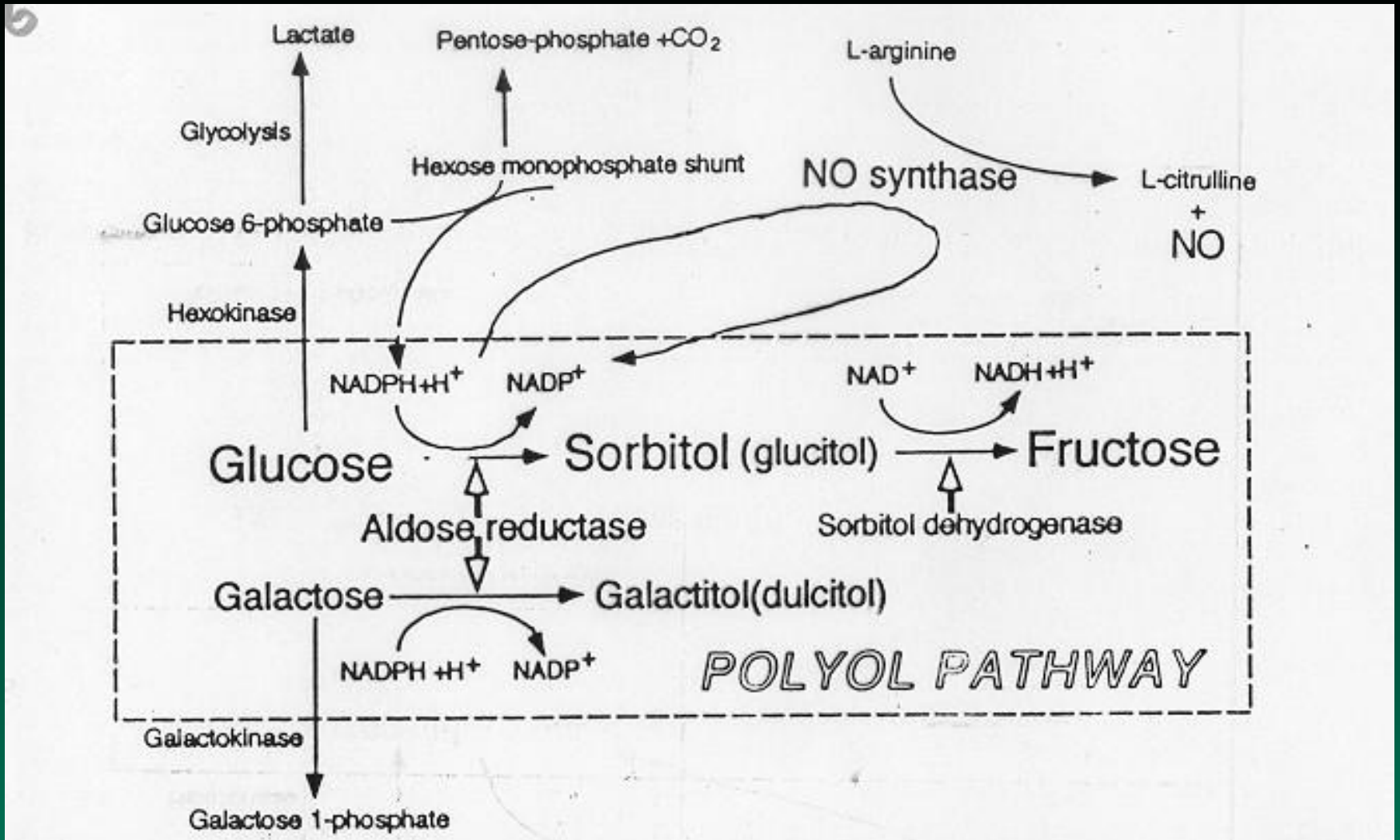


Figure 1. Metabolic map of polyol pathway. Aldose reductase mediates the conversion of glucose to sorbitol using NADPH as a coenzyme, which is supplied by hexose monophosphate shunt. This coenzyme is considered to be used for the production of NO synthase. Excessive flux of polyol pathway therefore induces reduction of NO production by consumption of NADPH.

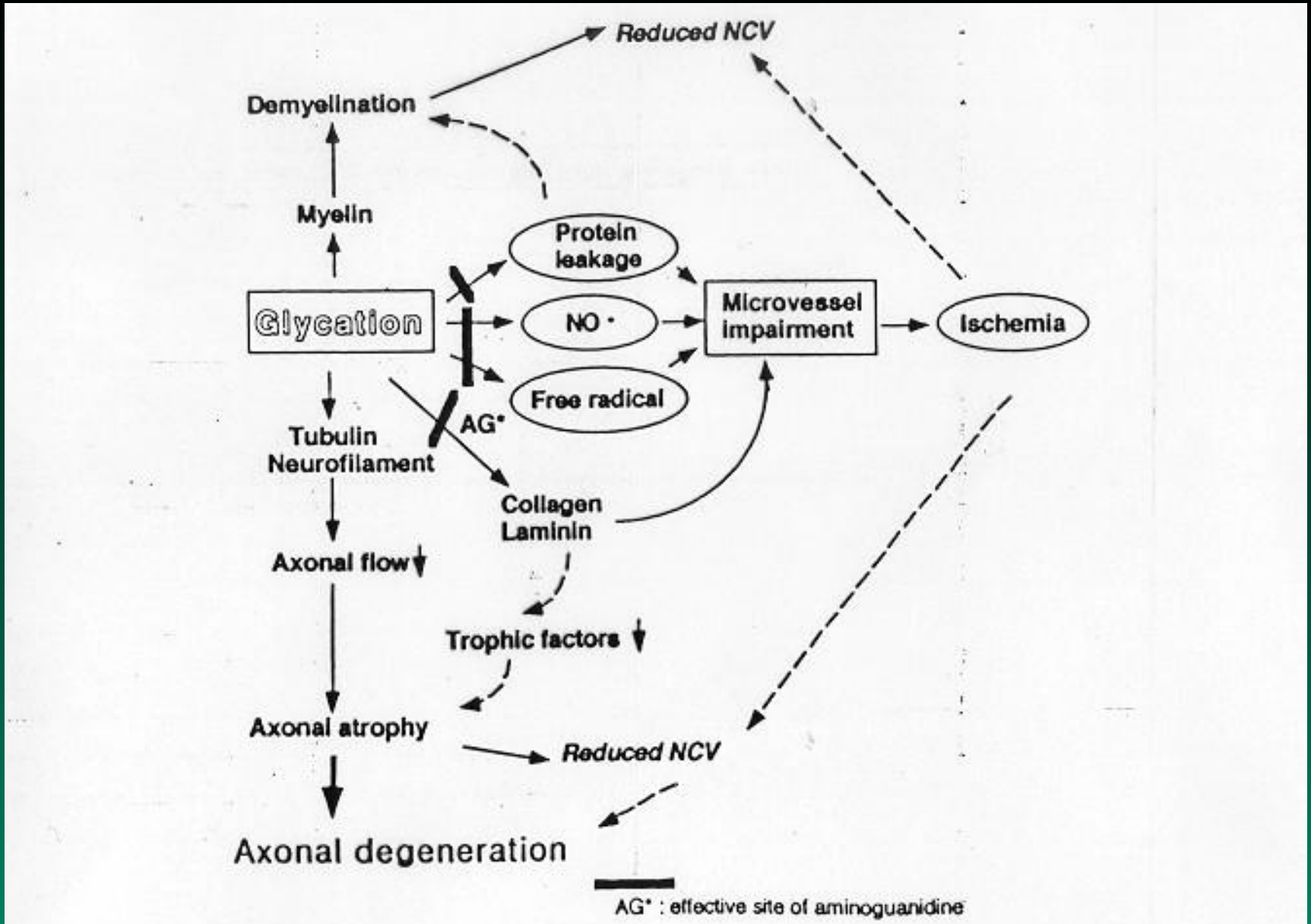


Figure 6. Schematic view of the mechanisms of how the excessive non-enzymatic glycation of neural proteins is involved in the pathogenesis of diabetic neuropathy.

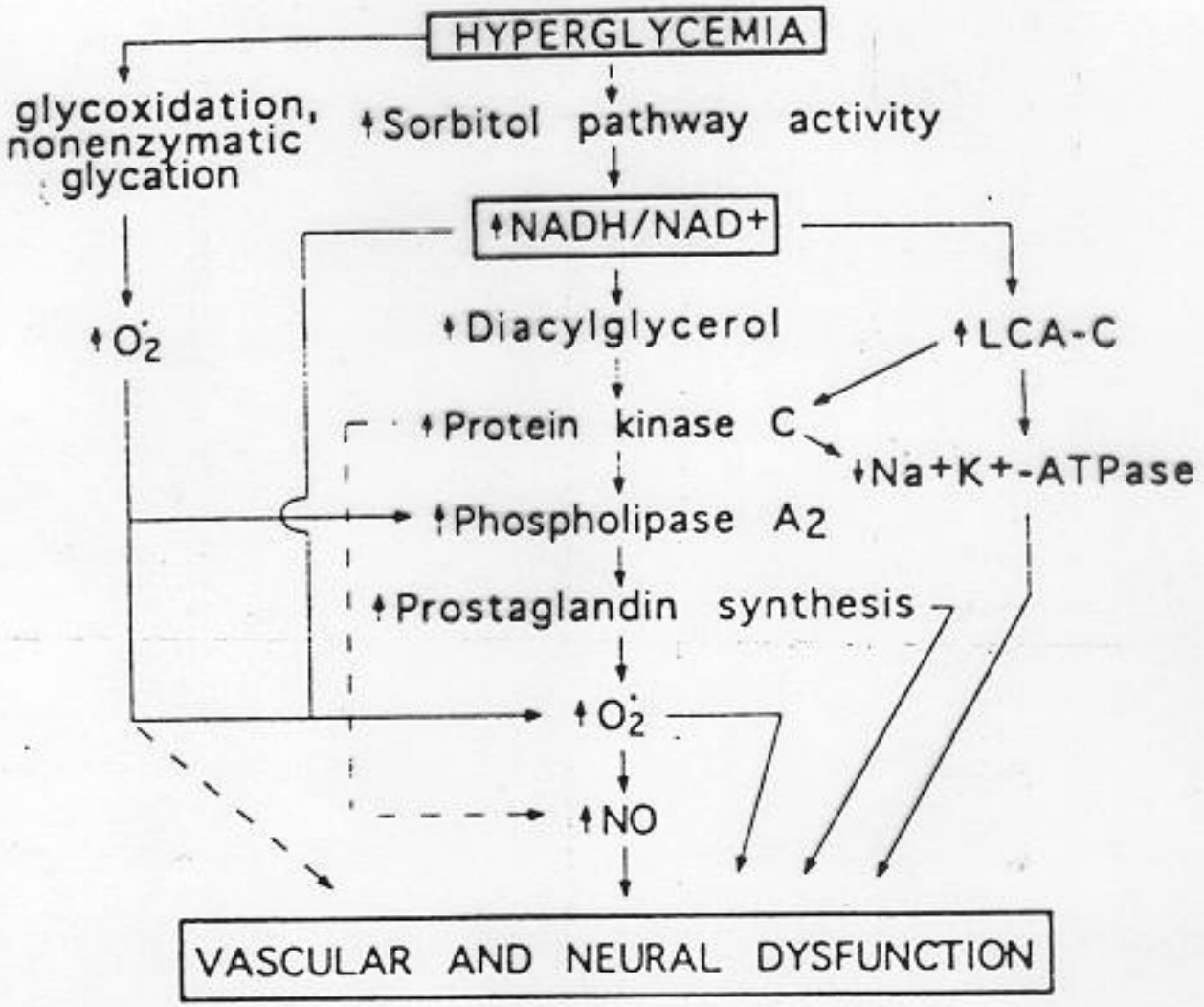


Figure 1. Tentative scenario for linkage of metabolic imbalances that mediate the effects of hyperglycaemic pseudohypoxia on vascular and neural dysfunction. $O_2^{\cdot}$; superoxide anion; NO, nitric oxide; LCA-C, long-chain acyl acid ester of carnitine. From ref. 40 with permission. Copyright American Diabetes Association.

Functional consequences:

- abnormalities in motor nerve function (in advanced stages of DM)
- sensory nerve conduction is impaired
- autonomic neuropathy (diabetic diarrhea, orthostatic hypotension....)

Possible mechanisms involved in development of DN

- blood supply to nerves is decreased because of microvascular damage (vasa nervorum may be damaged)
- energy source for normal rest membrane potential maintain is insufficient
- increased accumulation of sorbitol and fructose, decreased concentration of myoinositol
- non-enzymatic glycation of proteins

2. Diabetic micro- and macroangiopathies

Main functions of vascular endotelium

- regulates vascular tone and permeability
- regulates the balance between coagulation and fibrinolysis
- regulation of subendothelial matrix composition
- influences extravasation of leucocytes
- influences the proliferation of vascular smooth muscle and renal mesangial cells

To curry out these functions, the endothelium produces components of extracellular matrix and variety of regulatory mediators

A) Microvascular disease - specific lesion of DM that affect capillaries and arterioles of the retina, renal glomeruli, peripheral nerves, muscles and skin

Characteristic lesion :

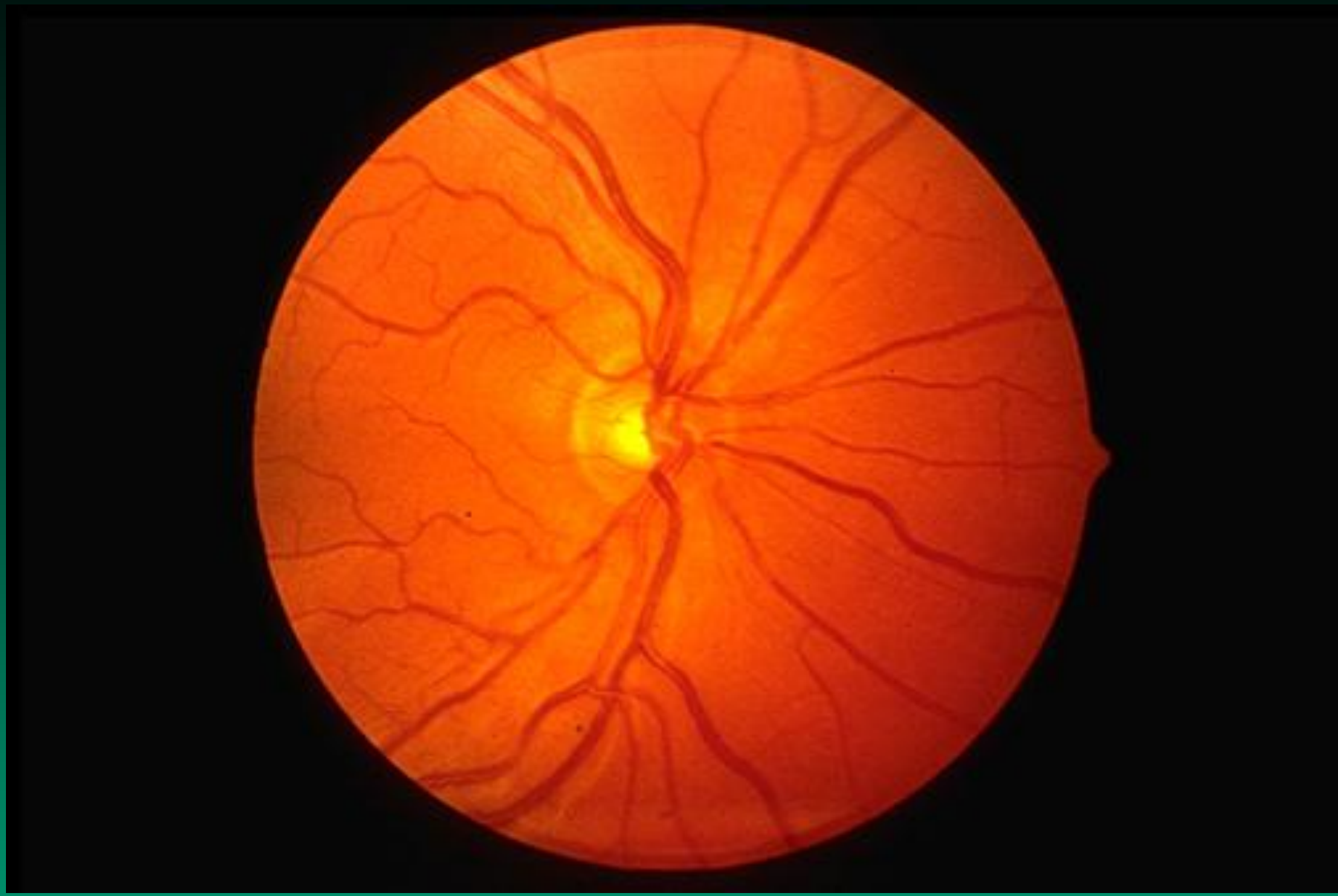
- thickening of the capillary basement membrane
- increased accumulation of glycoprotein in wall of small arteries and capillaries

a)Retinopathy - it is the result of retinal ischemia caused by microangiopathy

Pathomechanisms involved in retinopathy occurence:

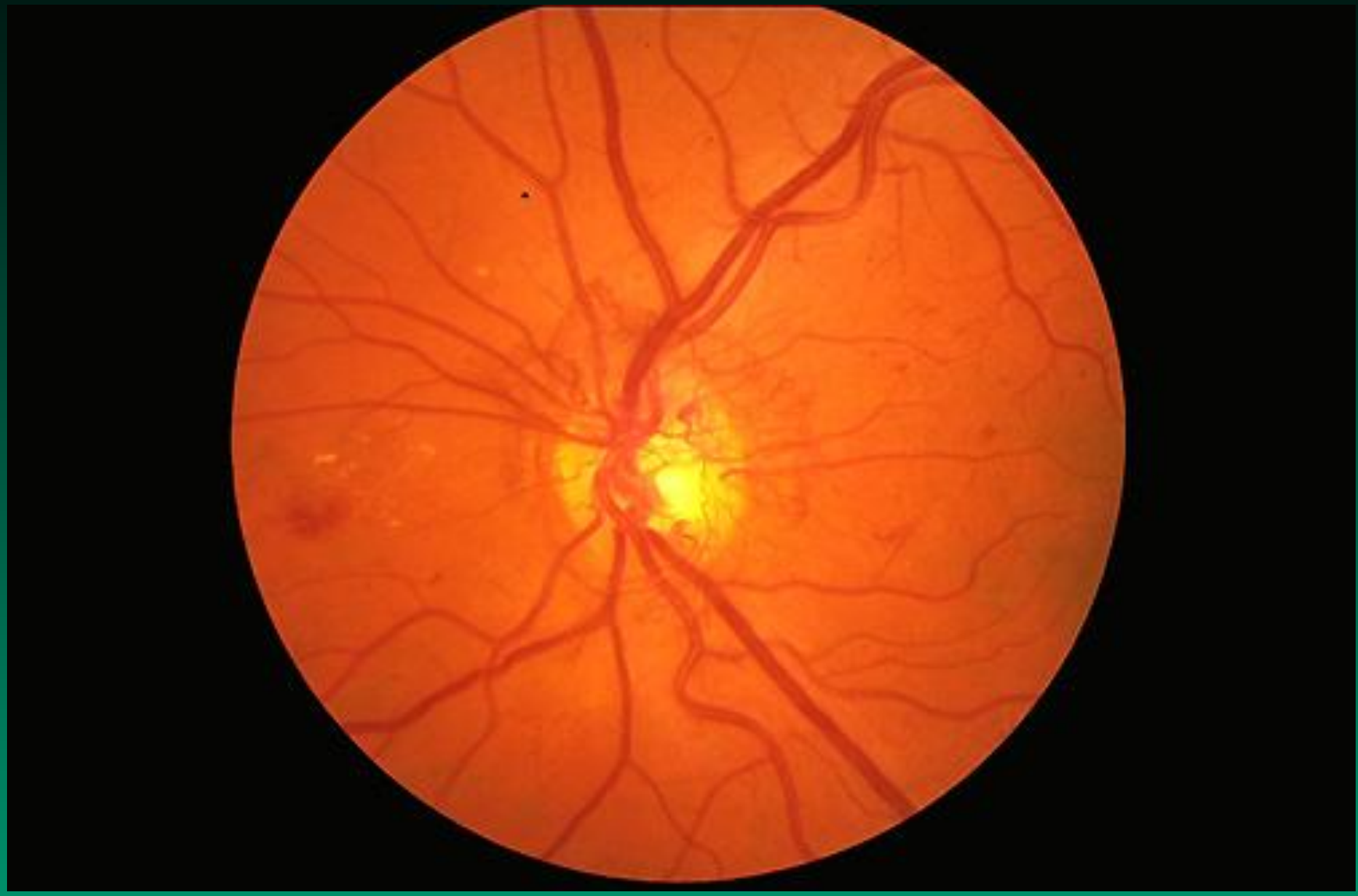
- increased retinal capillary permeability, vein dilation
- microaneurism formation and hemorrhages
- narrowing of small arteries lumen
- neovascularisation and fibrous tissue formation within the retina
- retinal scars formation → blindness

Vessels in retina in healthy man



Diabetic retinopathy – hard exudates, dot-and-blot hemorrhages, hard exudates attacks the fovea, cotton-wool patches,microaneurysms

Diabetic retinopathy – neovascularisation of neural target



b) Nephropathy - **it is the result of glomerular changes caused by DM**

Pathologic processes involved in diabetic nephropathy:

- **glomerular enlargement**
- **glomerular basement membrane thickening**

↓

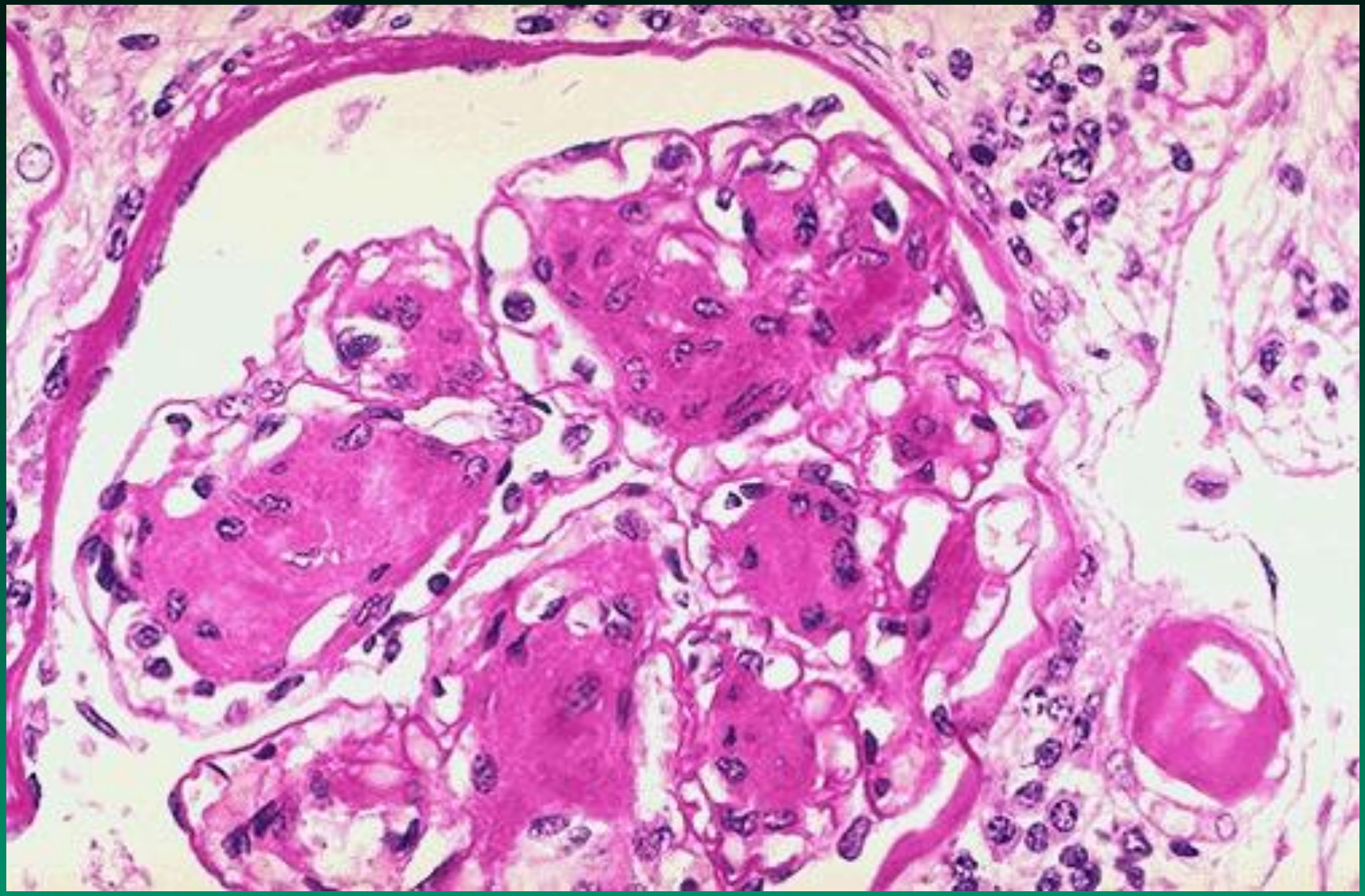
- **systemic hypertension often occurs**
- **neuropathy - see at B1.**

- **diffuse intercapillary glomerulosclerosis**

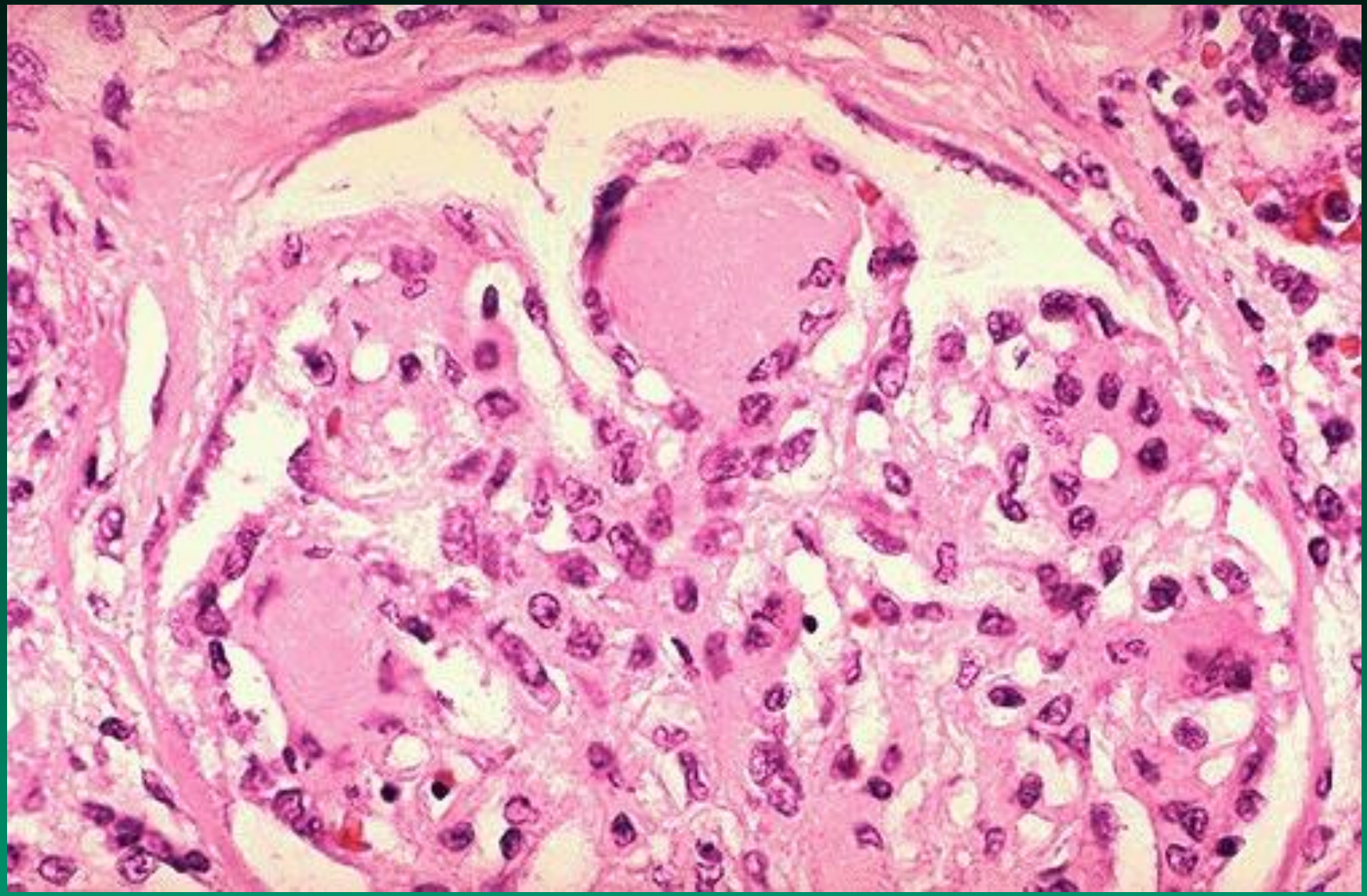
↓

proteinuria (more than 0.3g/day)

Diabetic nephropathy - nodular glomerulosclerosis and hyalinic atherosclerosis of small artery



Diabeti changes of glomerulus – advanced changes of the glomerulus



B) Macrovascular disease - atherosclerotic lesion

of larger arteries (coronary arteries, brain arteries, peripheral arteries)

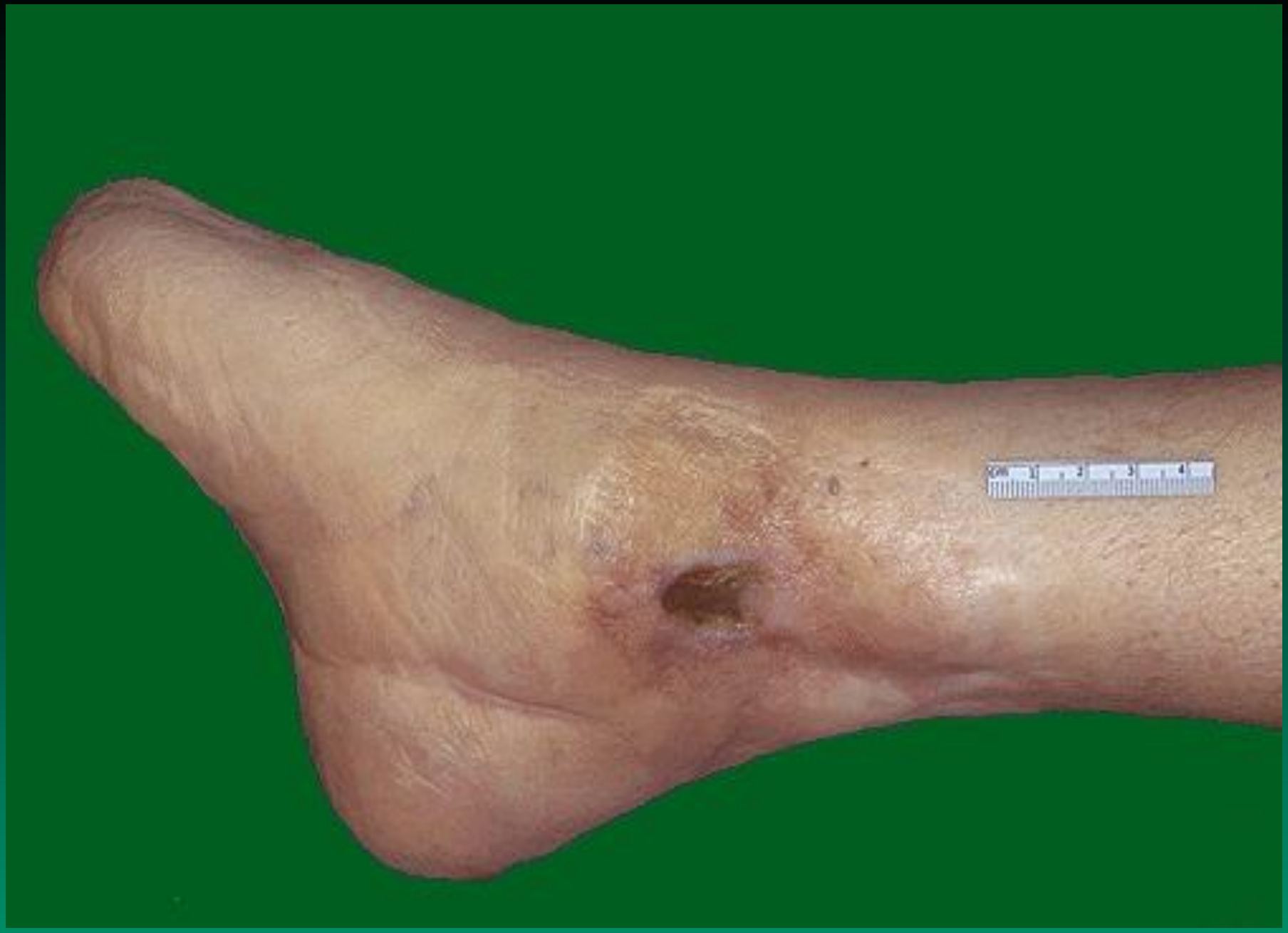
Main biochemical disturbancies leading to macrovascular disease:

- **accumulation of sorbitol in the vascular intima**
- **hyperlipoproteinemia → vascular abnormality in blood coagulation, occlusion by thrombus, accelerated atherosclerosis**

a) **Coronary artery disease → acute or chronic myocardial ischemia and/or infarction**

b) **Stroke → acute or chronic cerebral ischemia**

c) **Peripheral vascular disease → gangrene and amputation (diabetic foot)**



3. Infection

Persons with DM are at increased risk for infection

throughout the body.

Causes:

- disturbancies of senses (neuropathy, retinopathy) → decreasing the function of early warning system → breaks in skin integrity

- tissue hypoxia (macro- and microangiopathy)

- increased level glucose in body fluids → pathogens are able to multiply rapidly

- white blood cells supply to the tissue is decreased

- function of white blood cells is impaired

Diabetic nephropathy- infection present in renal pelvis