Diabetes mellitus and biochemical examination in patients with diabetes

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Definition

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (definition of American Diabetes Associacion, 2014).

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Prevalence of diabetes mellitus in the Czech Republic

- As of 31. 12. 2017 - 936 124 patients with diabetes, 91.8 % classified as T2DM
- The number of patients with diabetes in CR has doubled over last 20 years
- The absolute number of patients with T2DM is increasing leading to increased prevalence of long-term vascular complications (both micro- and macrovascular)
- In addition to patients with diagnosed diabetes large number of T2DM patients remains undiagnosed

Typical clinical symptoms of diabetes

- Fatigue
- Polydypsia
- Polyuria
- Nycturia
- Blurred vision
- Weight loss
- Symptoms of diabetic complications (neuropathy, retinopathy, atherosclerotic complications)
- More frequent cutaneous or urogenital infections

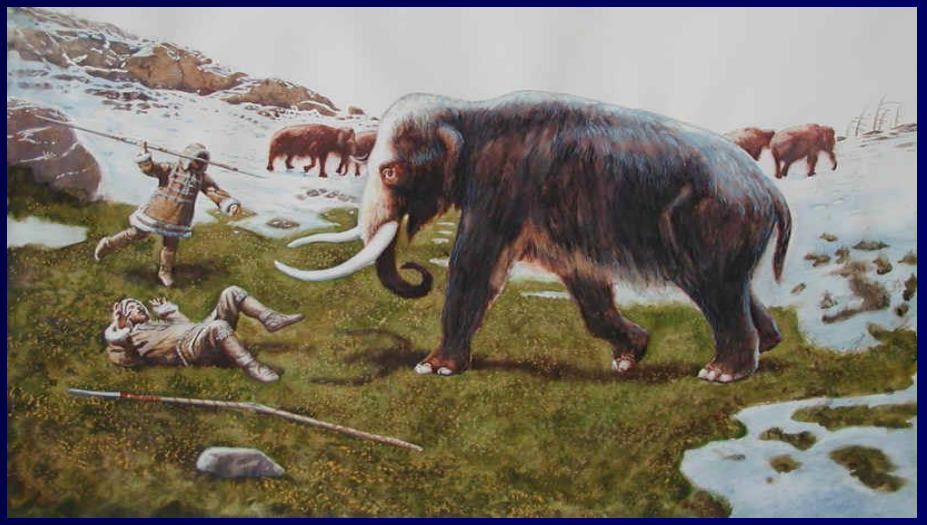
But…

- Typical symptoms are present mostly in patients with T1DM

- Majority of patients with T2DM has only modest or sometimes no aparent symptoms

The reasons for increased prevalence of diabetes

Thrifty genes



Lack of physical activity

Unhealthy diet

Stress

Classification of Diabetes

1. Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation)

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Criteria for the Diagnosis of Diabetes

Table 2.1—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

A1C ≥6.5 % (48 mmol/mol) *

- Performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay - www.ngsp.org
- POC testing not recommended
- Greater convenience, preanalytical stability, and less day-to-day perturbations than FPG and OGTT
- Consider cost, age, race/ethnicity, anemia, etc.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Prediabetes*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

* For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Recommendations: Screening for T2DM

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Recommendations: Monogenic Diabetes Syndromes

All children diagnosed with diabetes in the first 6 months of life should have genetic testing. B

- Consider Maturity-Onset Diabetes of the Young (MODY) in patients who have mild stable fasting hyperglycemia and multiple family members with diabetes not characteristic of T1DM or T2DM. E
- Consider referring individuals with diabetes that is not typical of T1DM or T2DM and occurs in successive generations to a specialist for further evaluation. E

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Criteria for Testing for T2DM in Children & Adolescents

- Overweight plus any 2 :
  - Family history of type 2 diabetes in 1st or 2nd degree relative
  - Race/ethnicity
  - Signs of insulin resistance or conditions associated with insulin resistance
  - Maternal history of diabetes or GDM
- Age of initiation 10 years or at onset of puberty
- Frequency: every 3 years
- Screen with A1C

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Diagnosis of Gestational Diabetes

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥140 mg/dL* (7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (55)	or	NDDG (56)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

Recommendations: Detection and Diagnosis of GDM

- Women with GDM history should have lifelong screening for development of diabetes or prediabetes at least every 3 years. B
- Women with GDM history found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes. A

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Metabolic syndrome

(Syndrom X, Insulin resistance syndrome, Ominous octet, Secret killer)

The cluster of clinical findings and biochemical abnormalities that increase the risk of atherosclerosis and related complications (myocardial infarction, stroke, peripheral artery disease etc.)

Diagnosis of metabolic syndrome (based on NCEP III (2001) + IDF criteria

Abdominal obesity: males ≥ 102 cm

females ≥ 88 cm

TGL ≥ 1,7 mmol/l or hypolipidemic therapy

HDL-cholesterol: males < 1.0 mmol/l

females < 1.3 mmol/l

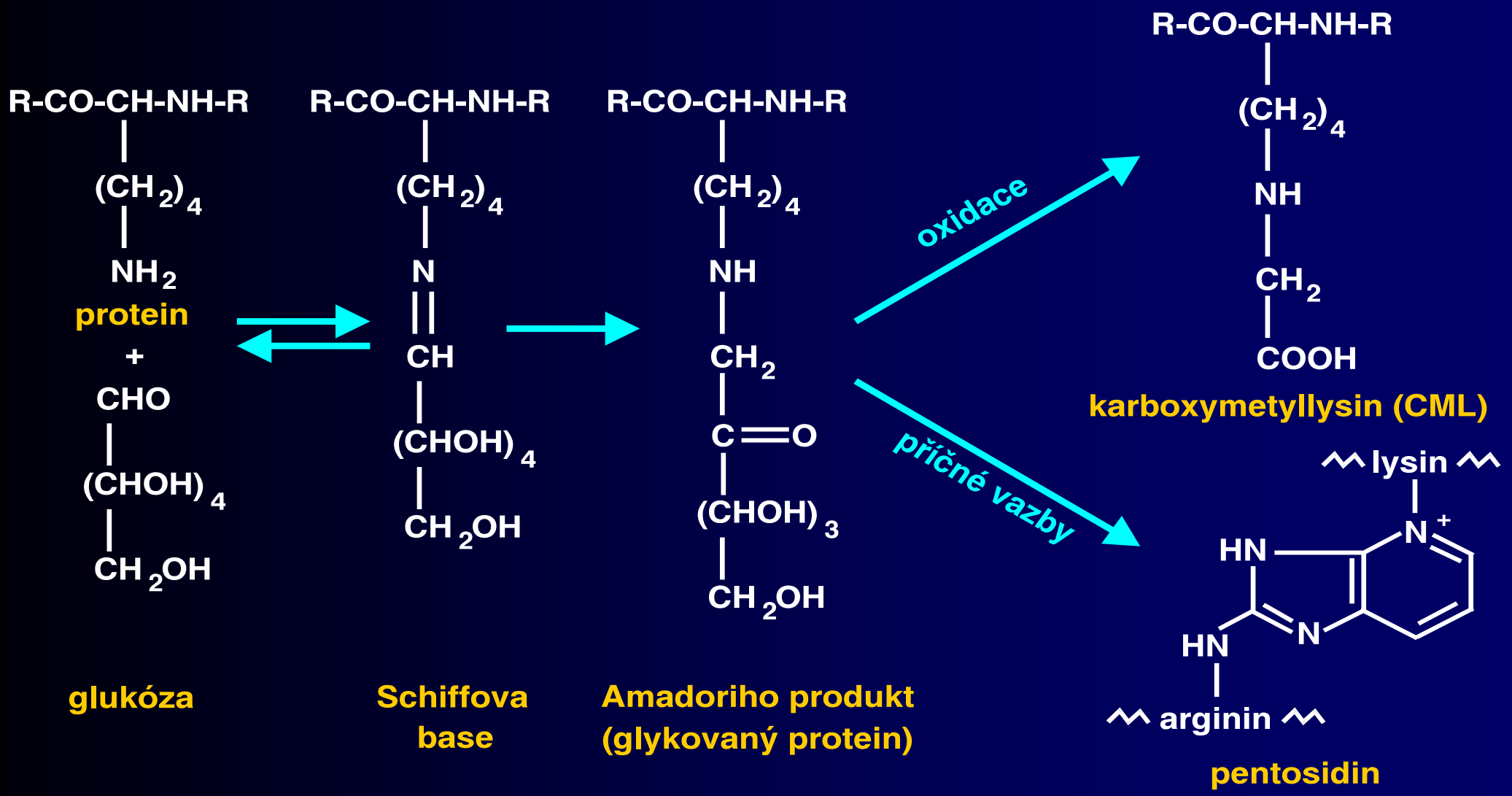
BP ≥ 130 / ≥ 85 mm Hg or antihypertensive treatment

Fasting blood glucose ≥ 5.5 mmol/l or IGT or T2DM

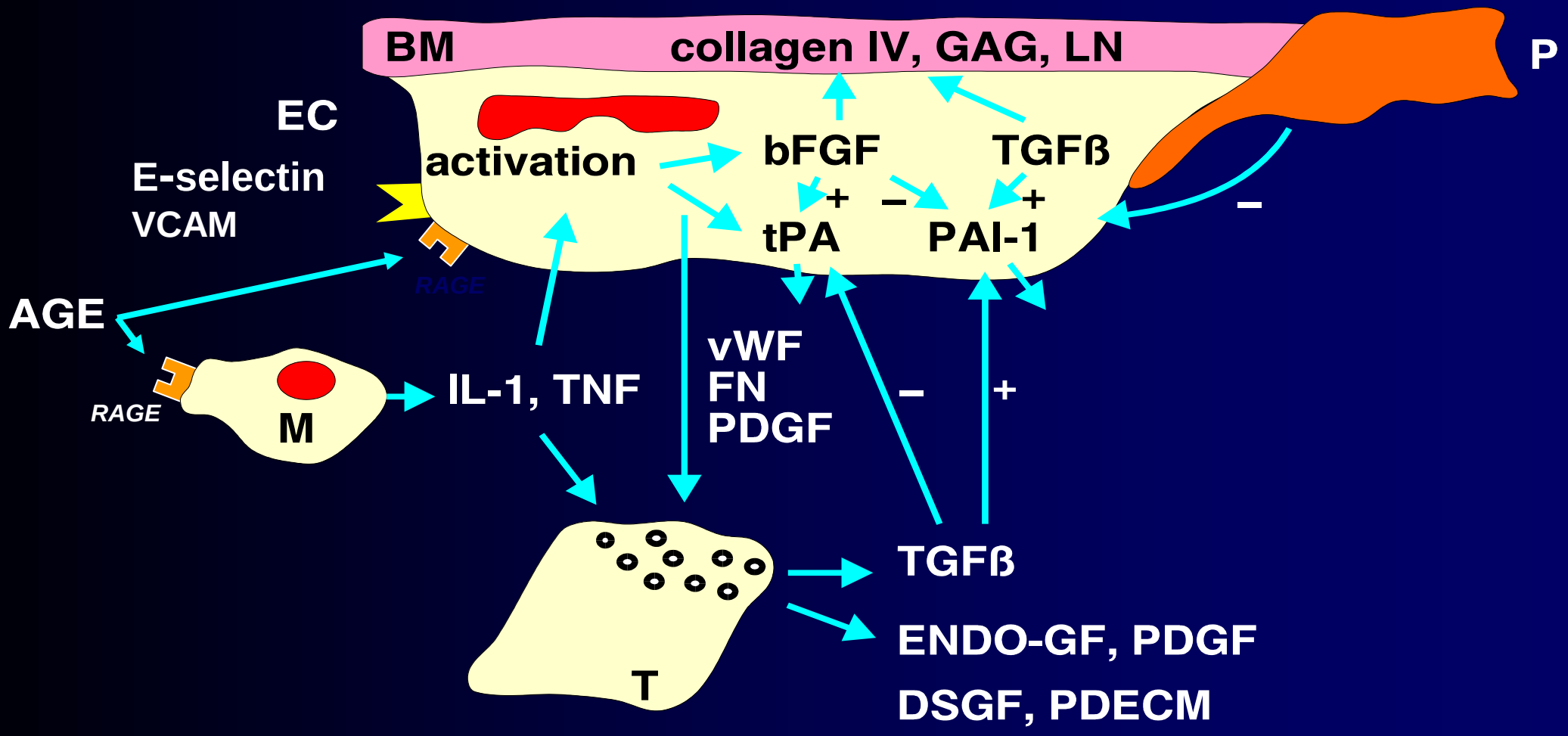
The ethiopathogenesis of complications differs in T1 and T2DM

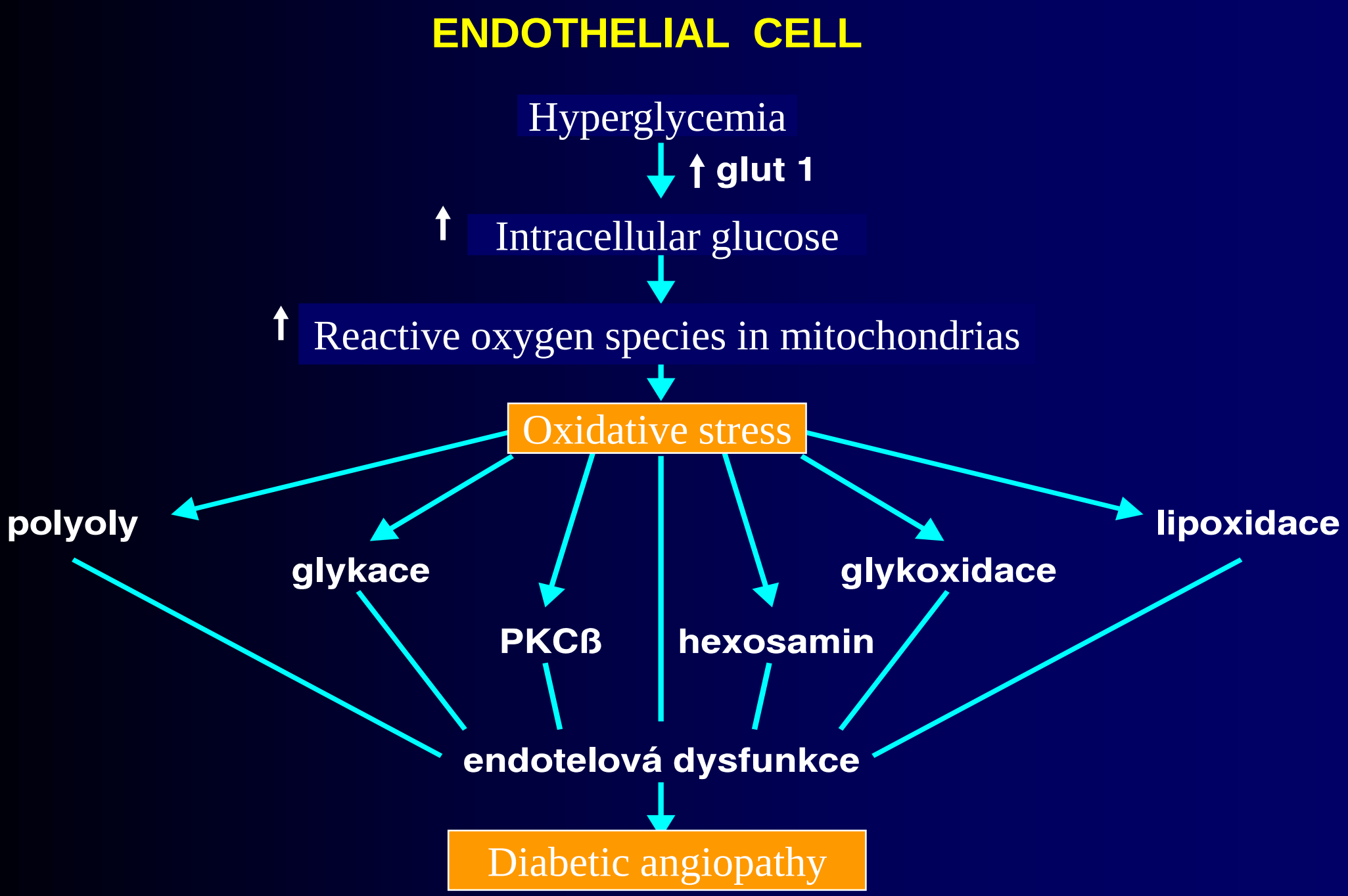
- In T1DM patients the primary pathology is chronic hyperglycemia without further accompanying complications (at the time of diagnosis)
- In T2DM the complications result from combination of chronic hyperglycemia and accompanying diseases such as obesity, dyslipidemia, arterial hypertension etc.), complications may be present at the time of diagnosis

Glycation and glycoxidation of proteins

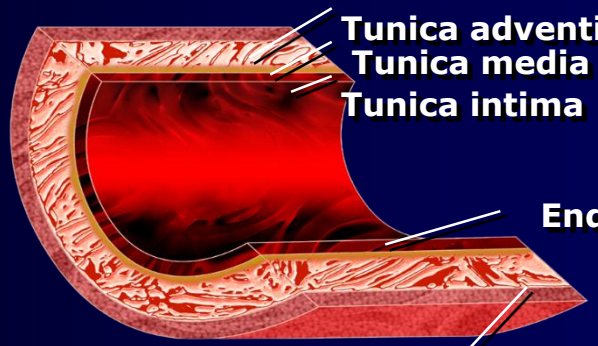


ENDOTHELIAL ACTIVATION IN DIABETIC PATIENTS




ENDOTHELIAL CELL
Hyperglycemia
glut 1
Intracellular glucose
Reactive oxygen species in mitochondrias
Oxidative stress
polyoly
glykace
PKCß
hexosamin
glykoxidace
lipoxidace
endotelová dysfunkce
Diabetic angiopathy

Insulin resistance and hyperinsulinemia lead to endothelial dysfunction



Endothelium derived Contracting factors

Endothelium derived Relaxing factors

TXA_2

Free Radicals

AngII

Endothelin

Contraction

Relaxation

Tone

+

-

+

-

Proliferation

Inhibition of Proliferation

Structure

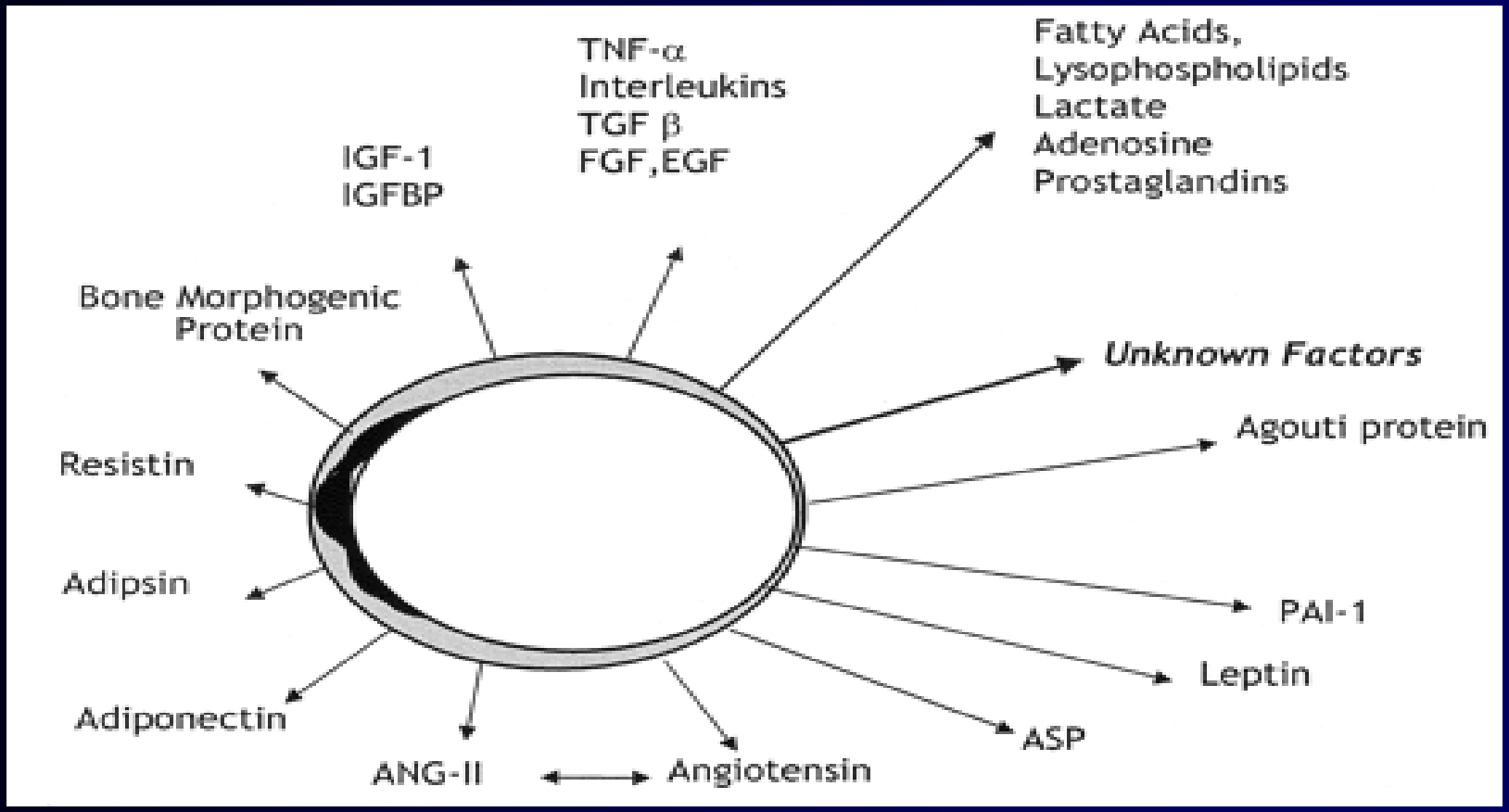
PGI_2

NO

EDHFI

C type NP

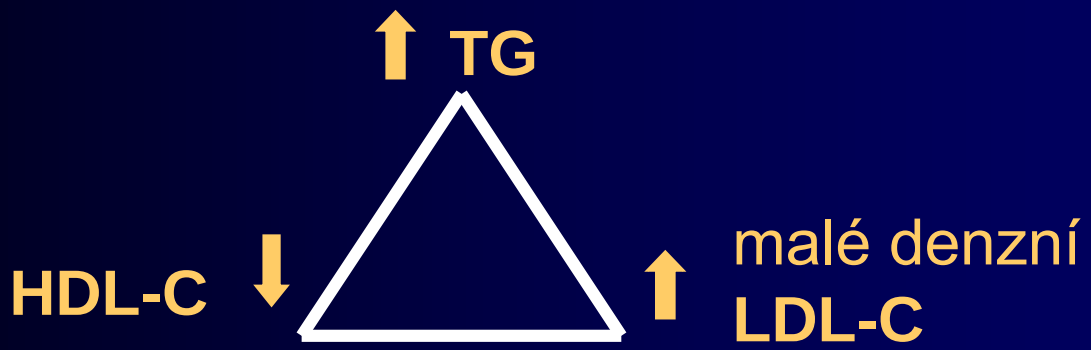
Adipose tissue as an endocrine organ

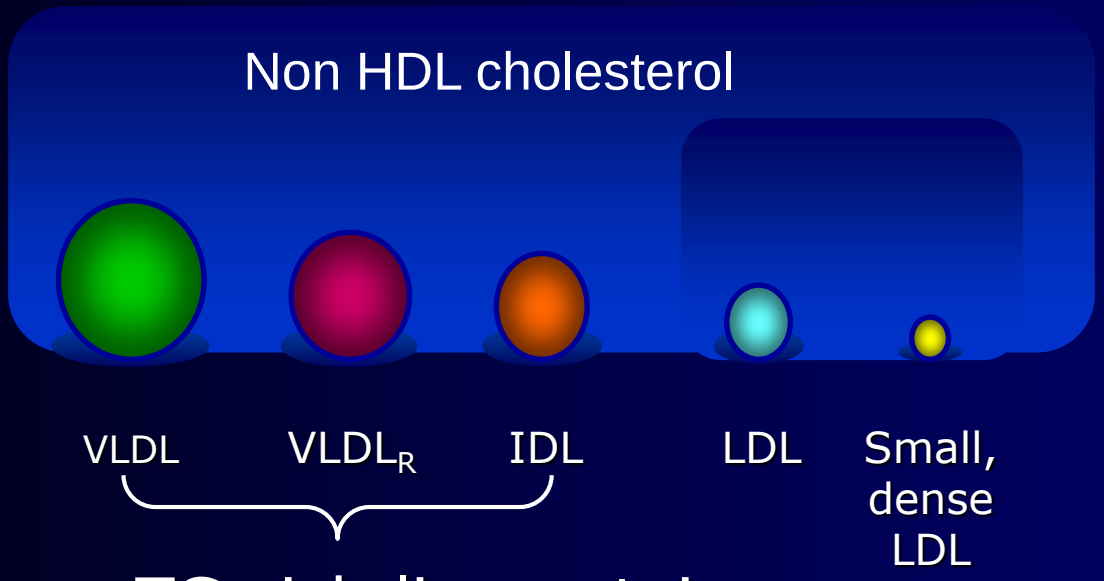


Ravussin et al, 2002

Metabolic syndrome and dyslipidemia

Lipidová triage





Complications of diabetes mellitus

- Acute
- Chronic

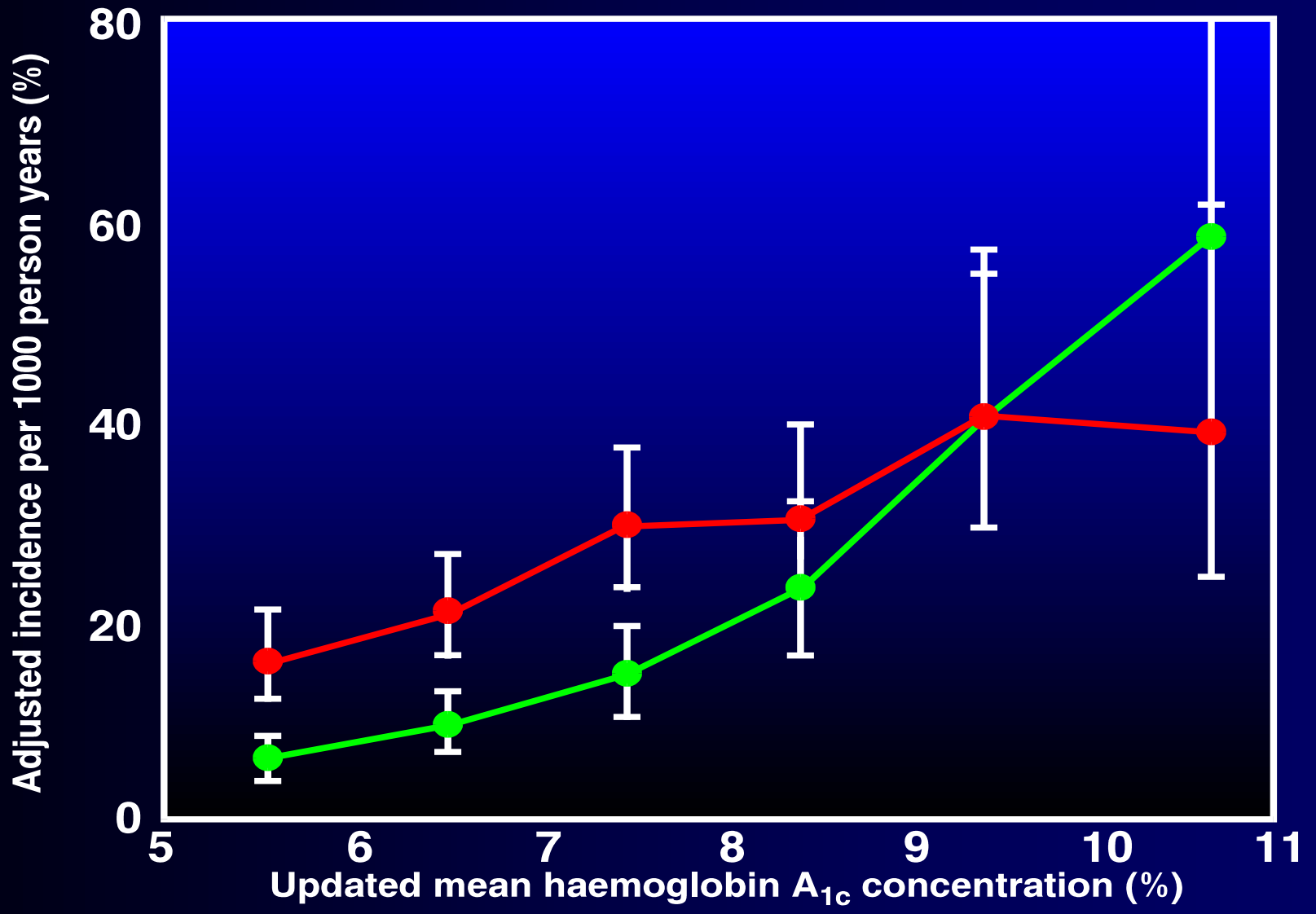
Acute:

- Ketoacidotic coma
- Hyperosmolar hyperglykemic coma
- Laktacidotic coma
- Hypoglycemia (hypoglycemic coma)

Chronic:

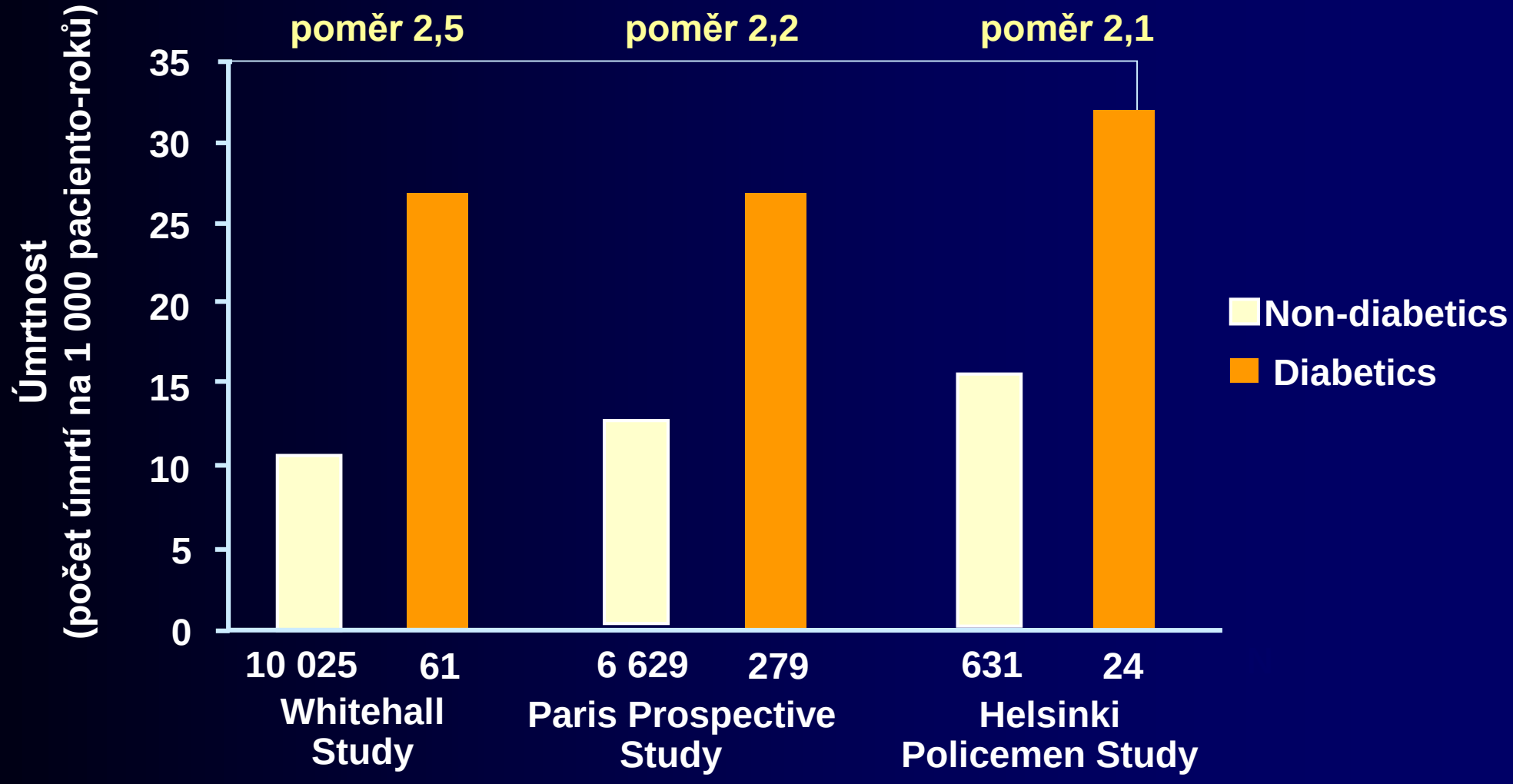
- makroangiopathic (accelerated atherosclerosis)
- mikroangiopathic (specific for diabetes)

MYOCARDIAL INFARCTION ● AND MICROVASCULAR END POINTS ● IN TYPE 2 DIABETIC PATIENTS



Stratton IM et al. (UKPDS), BMJ 321, 2000, 404-412

Mortality of diabetics is two-fold higher compared to non-diabetics



Balkau B, *et al*. *Lancet* 1997; 350:1680.

CHRONIC COMPLICATIONS OF DIABETES

a) Diabetic microangiopathy

Retinopathy

Nephropathy

Neuropathy - periopheral

- autonomic

b) Diabetic macroangiopathy

(= Atherosclerosis)

coronary heart disease, peripheral artery disease, cerebrovascular events

Mikroangiopathic complications of DM

- Diabetic nephropathy (one of the most common causes of renal failure)
- Diabetic retinopathy (the most common cause of blindness in developed countries)
- Diabetic neuropathy
- Diabetic foot – tissue damage (ulcerations, tissue necrosis) due to combination of diabetic neuropathy, micro- and macroangiopathy

DIABETIC NEUROPATHY

SOMATIC NEUROPATHY

(motoric, sensitive)

a) symetric neuropathy

lower limbs – pain x decrased sensitivity

b) focal and multifocal neuropathy

mononeuropathy, radiculopathy

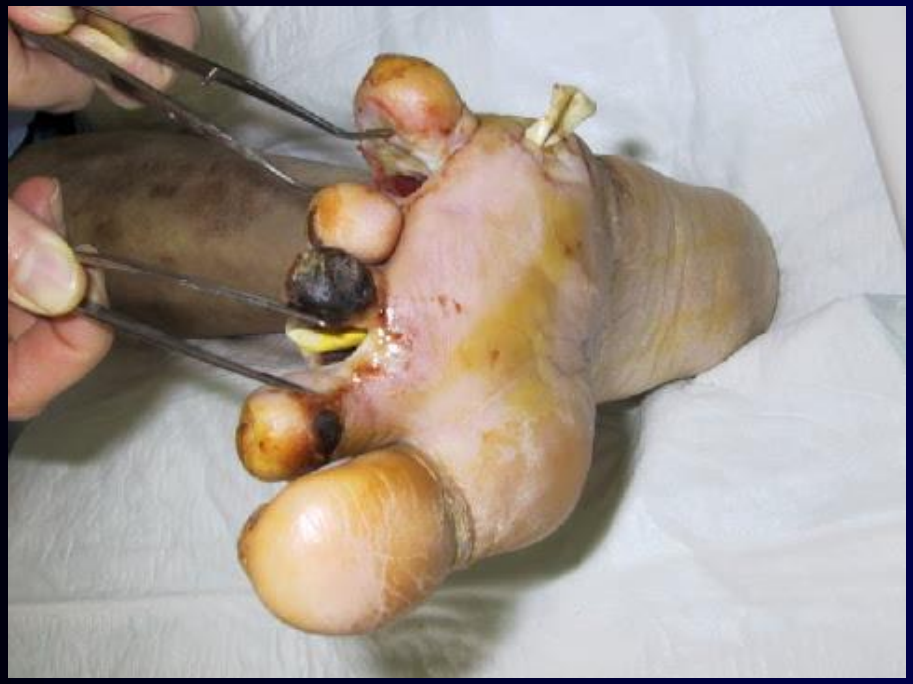
AUTONOMIC NEUROPATHY

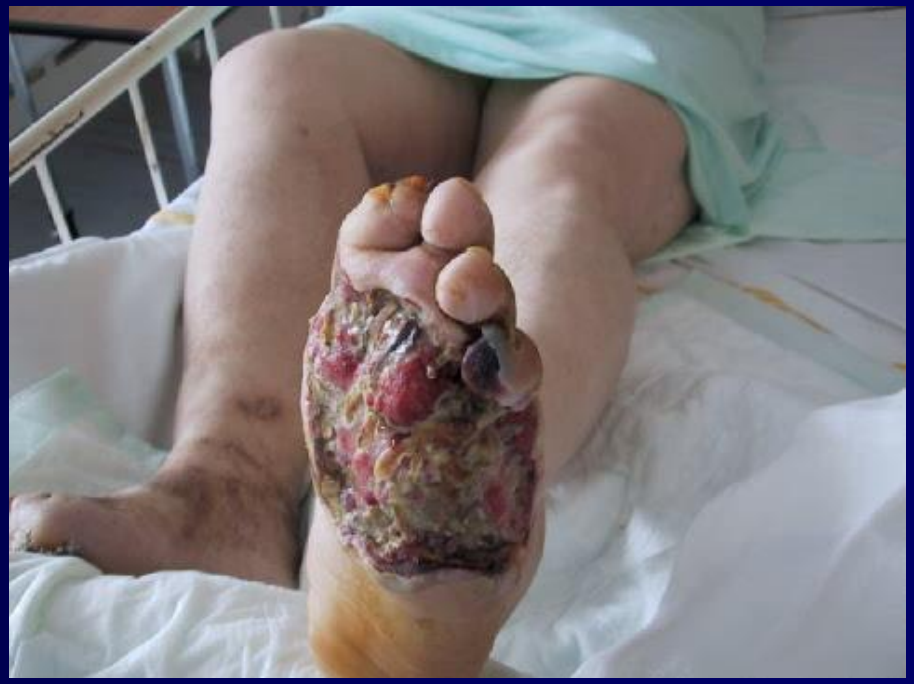
systems: cardiovascular, GIT, urogenital system

etc.

Diabetic foot syndrome

Combination of poor compensation, DM neuropathy, macro- and microangiopathy





Macroangiopathic complications of DM
ATHEROSCLEROSIS AND DIABETES

IHD-ischemic heart disease: 2-3x more common in diabetics than non-diabetics

CVE-cerebrovascular events : 3-5x more common in diabetics than non-diabetics

PAD-peripheral artery disease: 10-20x more common in diabetics than non-diabetics

All of the above mentioned diseases have in diabetic patients usually more severe and prolonged course and tend to have higher frequency of complications

Other complications or consequences of DM

- More common infections
- Dermal diseases (bullosis diabeticorum, infections)
- Diabetic cheiroarthropathy (joint pathology)
- Osteoporosis (both T1DM and T2DM)
- Sexual dysfunction
- Psychiatric diseases (depressions, anorexia nervosa, bulimia nervosa atd.)

Patophysiological mechanisms underlying T2DM

- Obesity
- Insulin resistance (muscle, liver, fat)
- Impaired endocrine function of pancreas
  - Relative insulin insufficiency
  - Gradual decrease of β-cell number
  - Qualitative impairment of the insulin secretion (missing 1. phase of insulin secretion)
  - Increased glucagon levels

Treatment of acute complications

- Hypoglycemia
- DKA (diabetic ketoacidosis)
- Hyperglycemic hyperosmolar syndrome
- Lactacidotic coma

Hypoglycemia

Decreased blood glucose (bellow 3.9 mmol/l)

- Mild (patient can treat himself)
- Severe (patient cannot treat himself)

Ethiology:

- Innapropriate dose of insulin or SU
-Increased physical activity
-Alcohol
-Renal of liver insufficiency
- Insulinoma (very rare)

Symptoms:

-Confusion (neuroglycopenia)
-Impaired vision
-Headache
-Nausea
-Tremor
-Sweating
-Tachycardia
-Nervousness
-Hunger

Hypoglycemia and activation of contraregulatory hormones

Blood glucose	Hormone
3,8-3,6 mmol/l	Glucagon
3,5-3,2 mmol/l	Catecholamines
3,1-2,7 mmol/l	Growth hormone
2,8-2,6 mmol/l	Cortisol

Treatment

Mild:

- 10-20 g of carbohydrates, repeat after 5-10 minutes if necessary

Severe:

- glucagon 1 mg s.c. or i.m.
- Glucose iv (40 % - ~50 ml)

Complications:

Falls/injuries
Brain damage
Sudden death (cardiac arrhytmias)
Posthypoglycemic hyperglycemia (Somogyi effect)
HAAF – hypoglycemia unawereness autonomic failure

Diabetic ketoacidosis

Definition

Acute complication of DM with incidence about 05/1000 patients DM and death rate of 20/100 000 people with DM

- Absolute or relative insulin deficiency and excess of glucose counterregulatory hormones (catecholamines, glucagon, cortisol, GH)
- May by present at the onset of T1DM

Etiology

- New onset of T1DM
- Innapropriate treatment (lack of insulin)
- Infections
- Stroke
- Operations, severe injuries
- Uncertain (about 50 %)

Pathogenesis and clinical presentation

Increased ketogenesis in liver due to lack of insulin (→acetoacte, beta-3-hydroxybutyrate)

- Hyperglycemia
- Hypeketonemia
- Metabolic acidosis, increased anion gap
- Dehydration
- Potassium deficiency (blood potassium levels may be normal or even increased)
- Increased FFA, TGLs, cholesterol
- Hypernatremia
- Leukocytosis
- Increased amylase

- Extreme thirst
- Polyuria
- Polydypsia
- Nausea, vomiting
- Abdominal pain
- Hypotension
- Dyspnoea
- Weakness
- Hyperpnoea (Kussmaul breathing)
- Unconsciousness

Treatment of DKA

- Rehydration (isotonic 0,9 % NaCl – 500-1000 ml/1 hour, 500 ml next 6 hours, 500-250 ml/hour for next 12 hours) – total fluids 8-12 l/24 hours
- Potassium supplementation – 20 mmol/hour initially
- Insulin treatment – bolus 5-10 IU i.v, 5-10 IU continuously – blood glucose drop by 2-3 mmol/hour
- General supportive ICU care and monitoring of vital functions
- Bicarbonate usually not necessary
- Too quick drop of blood glucose (e.g. 8-10 mmol/hour) might be dangerous – brain edema

Complications: renal failure
cardiac arthytmias
infections
stroke
venous thrombosis

Hyperglycemic hyperosmolar syndrome

Acute complication of T2DM with severe prognosis (>50 % mortality)

Etiology: fluid deficiency due to osmotic diuresis (stroke, infections, cardiacv failure)

Symptoms: polydypsia, polyuria, unconsciousness, hyperglycemia, hypersomolarity, metabolic acidosis, renal failure

Treatment: rehydration (~10 l deficiency), i.v. insulin administration, potassium supplementation, general ICU supportive care and vital functions monitoring

Complications: renal failure, cardiac failure, thrombosis, infections

Poor prognosis – elderly polymorbid patients

Lactic acidosis

Metabolic acidosis due to excessive lactate accumulation

Type A: with tissue hypoxia – cardiac failure, anemia, COPD, shock

Type B: without tissue hypoxia (e.g. toxins- or drug-induced - fenformin)

Increased lactate levels: > 7 mmol/mol (normal < 2 mmol/mol), metabolic acidosis, hypotension, coma

Treatment and complications are similar to hyperglycemic hyperosmolar syndrome

Poor prognosis – elderly polymorbid patients

Examination at the time of diagnosis of T2DM

Medical history:

- - disease symptoms,
- - risc factors of atherosclerosis (smoking, hypertension, obesity, hyperlipoproteinemia, including family history)
- - dietary habits, nutritional status
- - physical activity
- - current therapy
- - the presence of other diseases with possible connection DM
- - frequency, severity and causes of acute complications
- - psychosocial and economical factors influencing the therapy,
- - family history of DM and other endocrine disorders
- - disease that can cause secondary diabetes

Examination at the time of diagnosis of T2DM

Physical examination:

- - body weight, height, BMI, waist circumference
- - blood prressure
- - heart examination, heart rate
- - skin examination
- - thyroid gland examination
- - examination of upper and lower limb arteries
- - ophtalmological examination (fundoscopy),
- - cursory neurological examination of lower limbs

Examination at the time of diagnosis of T2DM

Laboratory examination:

- - fasting and postprandial blood glucose
- - lipids (total cholesterol, HDL a LDL cholesterol, triaglycerides),
- - Na, K, Cl, Ca, phosphates, urea, creatinine, uric acid, ALT, AST, ALP a GMT,
- - glycated hemoglobin (HbA1c),
- - urine: glucose, protein, ketones semiquantitatively, urine sediment, urine culture
- - C-peptide
- - TSH

Other examination:

- ECG

Treatment targets

Tab. 1. Cíle léčby nemocného s diabetem

Ukazatel		Požadovaná hodnota
HbA1c(%)*		< 4,5 (<6,0)
Glykémie v žilní plazmě	nalačno/před jídlem (mmol/l)	≤ 6,0 (<7,0)
Hodnoty glykémie v plné	kapilární krvi (selfmonitoring)	
	nalačno/před jídlem (mmol/l)	4,0–6,0 (<8,0)
	postprandiální (mmol/l)	5,0–7,5 (<9,0)
Krevní tlak (mmHg)		< 130/80
Krevní lipidy		
celkový cholesterol (mmol/l)		< 4,5
LDL cholesterol (mmol/l)		< 2,5
HDL cholesterol (mmol/l) : muži /ženy		> 1 / > 1,2
triacylglyceroly (mmol/l)		< 1,7
body mass index **		19-25
obvod pasu: ženy (cm) / muži (cm)		< 80 /< 94
Celková dávka inzulinu/24 hodin/kg hmotnosti (IU)		< 0,6

* HbA_{1c} - glykovaný hemoglobin –podle IFCC s normálními hodnotami do 4 %

** u nemocných s nadváhou a obezitou je cílem redukce hmotnosti o 5-10 % a následně ji udržet

*** u diabetiků po kardiovaskulární příhodě LDL cholesterol pod 2,0 mmol/l

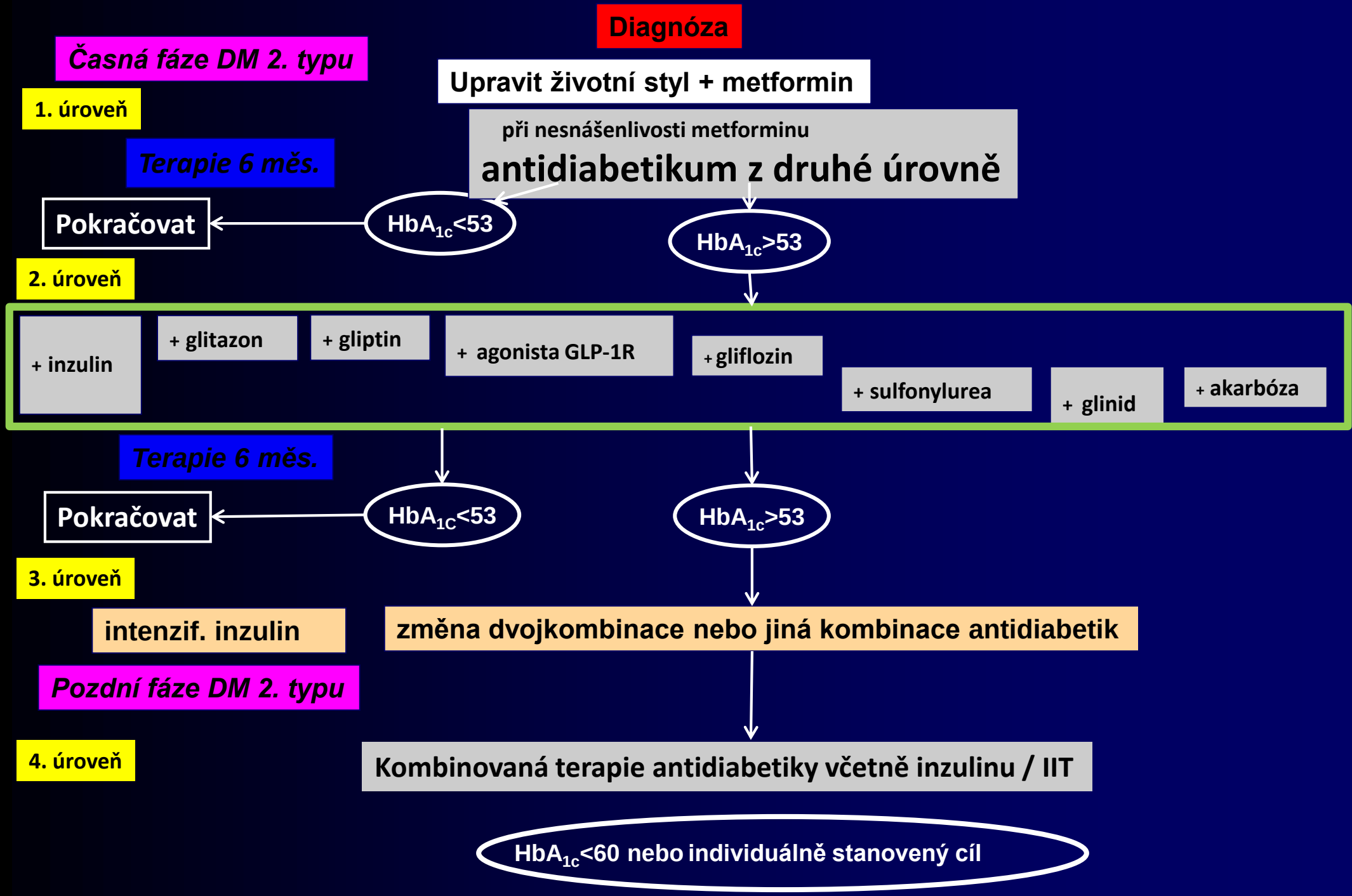
Treatment plan of T2DM patient

- Individual dietary regimen recommendation
- Lifestyle changes (increased physical activity, smoking cessation),
- Individualized aims and targets
- Education of patients and family members
- Pharmacological treatment of diabetes and accompanying diseases
- Psychosocial care

Major principles:

The overall goal is to prevent or delay the development of micro- and macrovascular complications

- Early diagnosis and intensive pharmacological treatment immediately after diagnosis (metformin) – target Hb1Ac – 45 mmol/mol
- In patients with long history of T2DM and unsatisfactory control the targets should be less ambitious (Hb1AC 53-70 %)
- Avoid hypoglycemia, weight gain
- Intensive life-style measures and education of patients (diet, ↓body weight, ↑ physical activity)
- Intensive intervetion of CV risk factors (BP, lipids, smoking cessation)

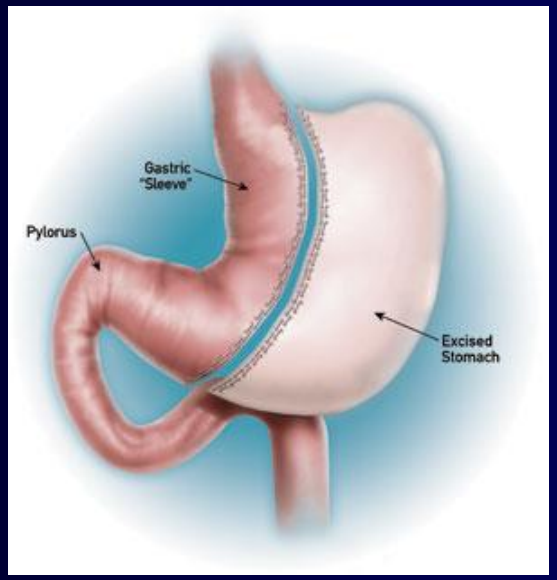

Diagnóza
Časná fáze DM 2. typu
Upravit životní styl + metformin
1. úroveň
při nesnášenlivosti metforminu
antidiabetikum z druhé úrovně
Terapie 6 měs.
Pokračovat
HbA1c<53
HbA1c>53
2. úroveň
+ inzulin
+ glitazon
+ gliptin
+ agonista GLP-1R
+ gliflozin
+ sulfonylurea
+ glinid
+ akarbóza
Terapie 6 měs.
Pokračovat
HbA1C<53
HbA1c>53
3. úroveň
intenzif. inzulin
změna dvojkombinace nebo jiná kombinace antidiabetik
Pozdní fáze DM 2. typu
4. úroveň
Kombinovaná terapie antidiabetiky včetně inzulinu / IIT
HbA1c<60 nebo individuálně stanovený cíl

Bariatric/metabolic surgery in T2DM treatment

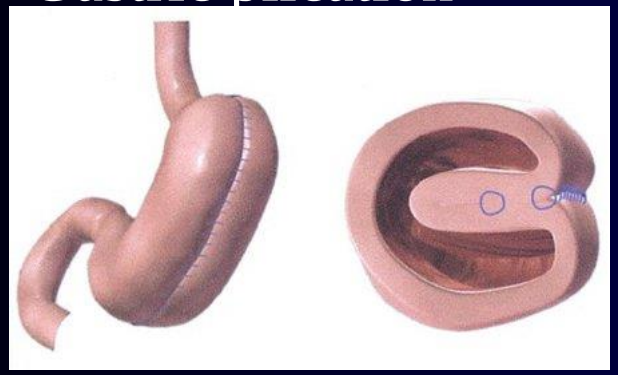
Restrictive

Gastric banding

Sleeve gastrectomy

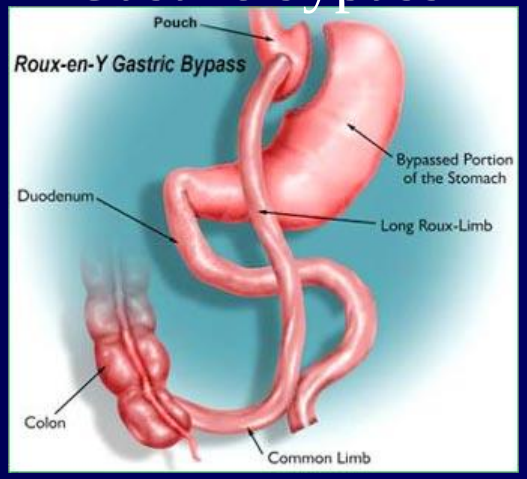


Gastric plication

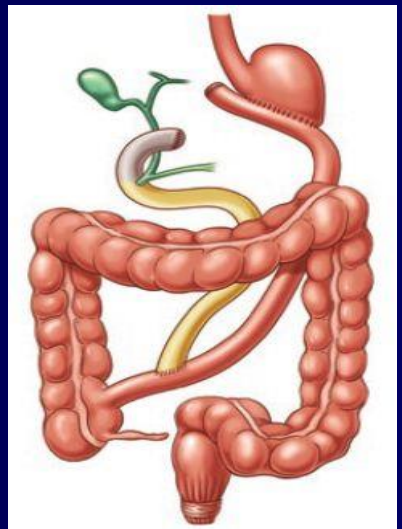


Malabsorbtive/combined

Gastric bypass



Biliopancreatic diversion



Basic principles of T1DM treatment:

1. Intensified insulin therapy – the only regimens mimicking closely physiological insulin secretion

2. Education – basic prerequisite for succesful diabetes treatment

3. Selfmonitoring – enables self-adjustment of insulin deses by the patient

Transplantation therapy in T1DM

- Isolated Langerhans islets transplantation
- Pancreas transplantation
- Combined pancreas and kidney transplantation

Only limited number of patients, very expensive, need of long-term immunosuppression therapy

But: long-term insulin independence, improvement of quality of life