

Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

**MANAGEMENT OF A PATIENT WITH
HYPERGLYCEMIA (DIABETES MELLITUS).
MANAGEMENT OF PATIENTS WITH
HYPOGLYCEMIC STATES**

Methodical recommendations
for preparation for practical training of higher medical
education applicants in the 6th year

Electronic resource

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M 24 **Management** of a patient with hyperglycemia (diabetes mellitus). Management of patients with hypoglycemic states : methodical recommendations for preparation for practical training of higher medical education applicants in the 6th year : methodical recommendations [Electronic resource] / compilers T. M. Tykhonova, O. V. Kanishcheva, N. Ye. Barabash, I. V. Soldatenko, Ye. V. Simonova, O. Yu. Bychkova, L. O. Martymianova, N. V. Lysenko. – Kharkiv : V. N. Karazin Kharkiv National University, 2023. – (PDF 45 p.)

The methodical recommendations outline the issues of diagnosis and differential diagnosis of carbohydrate metabolism disorders, algorithms for the treatment of hyperglycemia, specific diabetes, and hypoglycemic states.

The preparation has been drawn up for practical training on the discipline «Internal Medicine» for 6th course students.

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ABBREVIATIONS AND ACRONIMS

ACTH	– adrenocorticotrophic hormone
ADA	– American Diabetes Association
BG	– blood glucose
BMI	– body mass index
CVD	– cardiovascular disease
DM	– diabetes mellitus
DPP-4	– Dipeptidyl peptidase IV
FBG	– fasting blood glucose
HbA1c	– glycated hemoglobin
HDL	– high-density lipoprotein
HOMA-IR	– Homeostatic Model Assessment for Insulin Resistance
HyperGl	– hyperglycemia
HypoGl	– hypoglycemia
GDM	– gestational diabetes mellitus
GLD	– glucose lowering drug
GLP-1	– glucagonlike peptide-1
GLT	– glucose lowering therapy
IFG	– impaired fasting glucose
IGT	– impaired glucose tolerance
IR	– insulin resistance
IT	– insulin therapy
LADA	– Latent Autoimmune Diabetes of Adults
OGTT	– oral glucose tolerance test
SGLT-2	– Selective sodium-glucose transporter-2
STH	– somatotrophic hormone
TZDs	– thiazolidinediones
WHO	– World Health Organization

1. REQUIRED BASIC KNOWLEDGE AND SKILLS

Names of previous disciplines	Acquired skills
Foreign Language	To be able to work with foreign literature to obtain data on modern methods of diagnosis and treatment of carbohydrate metabolism disorders
Medical informatics	To use modern softwear and to be able to evaluate and interpret results of clinical trials, to be able to work with electronic databases
Human anatomy. Normal physiology. Histology, cytology and embryology	To know the structure, functions and regulation mechanisms of endocrine system and its organs involved in maintaining glucose homeostasis; to understand and be able to determine the relationship of endocrine system with other organs and systems of a human body
Pathomorphology Pathophysiology	To know the basics of pathological processes: mechanisms of pathological processes development, changes in the human body, compensatory reactions, development of causal relationship in the entire organism pathology. To describe and schematically depict mechanism of hyper- and hypoglycemic states in various pathologies, to substantiate pathogenetic approaches to drug therapy
Propaedeutics of internal medicine	To perform physical examination of a patient, to analyze results of laboratory and instrumental methods. To be able to do differential diagnosis based on physical and additional data, formulate final diagnosis.
Pharmacology	To be able to navigate in the range of drugs. To know the mechanism of drugs action, their pharmacodynamics, indications, contraindications and side effects. To know clinical pharmacology peculiarities of drugs, used in diabetes mellitus and hypoglycemic conditions management, their pharmacological features in different subset of patients. To substantiate the choice of a drug and its treatment regimen taking into account the principles of evidence-based medicine, to be able to optimize the treatment regimen, to evaluate the effectiveness and safety of pharmacotherapy taking into account the individual characteristics of a patient, presence of comorbidities.

1.1. Student must know

- anatomy and functions of the endocrine system;
- relationship between organs and systems involved in maintaining glucose homeostasis;
- probable mechanisms of hyperglycemic and hypoglycemic states;
- classification of diabetes mellitus (DM) and other types of blood glucose abnormalities;
- acute and chronic complications of DM and their characteristics;
- diagnosis formulation in case of glucose metabolism disorders;
- DM diagnostic criteria;
- international guidelines and position statement on DM management;
- basics of hypoglycemia management.

1.2. Student must be able to

- to take history;
- to perform physical examination of a patient with carbohydrates metabolism disturbance;
- to assign the appropriate laboratory and instrumental tests and evaluate obtained results;
- to diagnose hyper- and hypoglycemic states using diagnostic criteria;
- to make differential diagnosis of hyperglycemia and hypoglycemia;
- to make clinical diagnosis on the basis of complaints, anamnesis, physical data and results of laboratory/instrumental investigations;
- to prescribe appropriate treatment in accordance with international protocols.

2. HYPERGLYCEMIA. DIAGNOSIS OF DIABETES MELLITUS

2.1. Introduction

Blood glucose (BG) is a widely used screening laboratory test thought to be one of the vital signs. Over the past few decades the prevalence of DM has risen significantly in nearly all countries and may be considered as a growing epidemic. Healthcare professionals of almost all specialties encounter patients with glucose metabolism disorders, so they have to have sufficient knowledge to differentiate this states and prescribe adequate therapy.

When hyperglycemia is left untreated, it can lead to many serious life-threatening complications that include damage to the eye, kidneys, nerves, heart, and peripheral vascular system. Thus, it is vital to manage hyperglycemia effectively and efficiently to prevent complications of the disease and improve patient outcomes.

2.2. Definition of hyperglycemia

The term «hyperglycemia» (HyperGl) is derived from the Greek *hyper* (*high*) + *glykys* (*sweet/sugar*) + *haima* (*blood*) and literally means an increase in BG levels. In a broader sense, it is a clinical condition characterized by high BG levels comparing with normal thresholds.

According to World Health Organization (WHO) the expected values for normal fasting blood glucose (FBG) concentration are between 70 mg/dL (3.9 mmol/L) and 100 mg/dL (5.6 mmol/L) (1 mmol/l = 18 mg/dl = 18 mg %).

In all cases, HyperGl is the predominance of the rate of glucose entry into the blood over the rate of its utilization.

2.3. Hyperglycemia types and mechanisms

HyperGl can be physiological and pathological.

1. *Physiological HyperGl* has adaptive value, providing delivery to tissues energy material that can be easily utilised. Such HyperGl always passes quickly.

1) Alimentary HyperGl. Appears after eating large amounts of easily digestible carbohydrates (sugar, candy, flour products, etc. etc.). Due to the fact that assimilation intake of the liver has certain limits, the simultaneous introduction of excess carbohydrates with food a part of the resorbed glucose enters the blood passing the liver, thereby causing food (alimentary) HyperGl. In case of alimentary HyperGl after 1.5–2 h after a meal, BG levels return to normal.

2) Neurogenic (or emotional) HyperGl. Develops with excitement, emotional arousal, severe pain. The stress response is largely mediated by the hypothalamic-pituitary-adrenal and sympatho-adrenal systems. The metabolic effects of cortisol include an increase in the concentration of BG as a result of gluconeogenesis activation in the liver and inhibition of glucose uptake by peripheral tissues such as skeletal muscle. Epinephrine and norepinephrine stimulate gluconeogenesis and glycogenolysis in the liver; in addition, norepinephrine has the additional effect of increasing the liver supply of glycerol as a results lipolysis activation.

2. *Pathological HyperGl* caused by a persistent violation of any link in the carbohydrate metabolism regulation.

1) Convulsive HyperGl (for epileptic seizures and tetanus).

2) Hormonal HyperGl, due to hyperproduction of counterinsular hormones: glucagon (glucagonoma), glucocorticoids (Cushing's syndrome/disease), catecholamines (pheochromocytoma), adrenocorticotrophic hormone (ACTH) (ACTH-secreted tumors), somatotrophic hormone (STH) (STH-secreted tumors), thyroid hormones (hyperthyroidism). Excess of these hormones lead to increase in BG concentrations as a result of gluconeogenesis stimulation (ACTH, glucocorticoids), glycogenolysis activation (glucagon,

catecholamines, thyroid hormones) or glycogen synthesis inhibition, despite normal or even increased blood level of insulin.

3) HyperGl in absolute or relative insulin insufficiency (DM).

4) Drug-induced HyperGl, which may be caused by nicotinic acid, phenytoin, adrenaline, caffeine, chlorpromazine treatment, the use of certain types of anesthesia (etheric, chloroformic, halogen-containing drugs), morphine, some anticancer drugs (eg, rituximab). The cause of HyperGl in these cases is the lipolysis, gluconeogenesis and glycogenolysis activation.

Pathological HyperGl can be constant or transient.

1. *Constant HyperGl* is a characteristic of DM, which can be a result of, among other causes, long-term use of glucocorticoids, STH, thyroid hormones.
2. The *transient form of HyperGl* disappears after the elimination of the causative factor(s) (for example, short-term use of the above drugs).

Plasma glucose test can be:

1. *Fasting*, i.e. on an empty stomach, determined by taking a blood sample from patients who have fasted for at least 8 hours. Current laboratory recommendations for BG measurement are to draw fasting blood samples in the morning rather than later in the day, as glucose levels tend to be higher in the morning than the afternoon.
2. *Postprandial*, i.e. 2 hours after eating.
3. *Random (casual)*, i.e. measured at any given point in the day. This assumes a recent meal and therefore has higher reference values. In a healthy person random glycemia never exceeds 11.0 mmol / l (200 mg / dl).

2.4. An algorithmic approach to hyperglycemia management. Diabetes mellitus classification and diagnostic criteria

American Diabetes Association (ADA) recommends screening for HyperGl adults aged 18 and older with overweight or obesity (according to ethnic criteria) and other risk factors (table 1). Additionally, all adults should be screened

for prediabetes and diabetes beginning at age 35. If tests are normal, screening should be repeated at a minimum of 3-year intervals.

Table 1

**Criteria for screening for DM or prediabetes in asymptomatic adults,
ADA, 2023**

1. Testing should be considered in adults with overweight or obesity (BMI ≥ 25 kg/m ² or ≥ 23 kg/m ² in Asian Americans) who have one or more of the following risk factors:
• First-degree relative(s) with diabetes
• High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
• History of CVD
• Hypertension ($\geq 140/90$ 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)
• Individuals with polycystic ovary syndrome
• Physical inactivity
• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (HbA1c $\geq 5.7\%$ [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. 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 and risk status.
6. People with HIV

BMI – body mass index, CVD – cardiovascular disease; HbA1c – glycosylated hemoglobin; GDM – gestational diabetes mellitus, IFG – impaired fasting glucose, IGT – impaired glucose tolerance, HDL – high-density lipoprotein, HIV – human immunodeficiency virus

American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S19–S40. <https://doi.org/10.2337/dc23-S002>

Glucose tolerance can be classified into three main categories: normal glucose homeostasis, DM, and impaired glucose tolerance (IGT), including impaired fasting glucose (IFG). Glucose tolerance is assessed by FBG measurement, response to oral glucose load (oral glucose tolerance test (OGTT)) and glycosylated hemoglobin (HbA1c) measurement, which shows the state of glucose metabolism in the last three months.

The management of patients with newly diagnosed HyperGl is presented on Fig. 1.

DM is a group of metabolic diseases characterized by hyperglycemia, as a result of insulin secretion or insulin action impairment or a combination of these factors, i.e. absolute or relative insulin deficiency. Chronic hyperglycemia in DM is accompanied by damage, dysfunction and insufficiency of various organs and systems.

DM is classified on the basis of the pathogenetic process caused hyperglycemia, in contrast to previously used criteria such as age of onset of the disease and type of treatment. There are two main categories of DM - type 1 and type 2. At the same time there are some other types of DM which may have signs of these both types. The both major types of DM have start in their pathogenesis with a phase of IGT, which in the case of DM type 1 immediately a transits to a phase of absolute insulin insufficiency, while the next stage in DM type 2 for a long time is a relative insulin insufficiency on a background of insulin resistance (IR) (fig. 2).

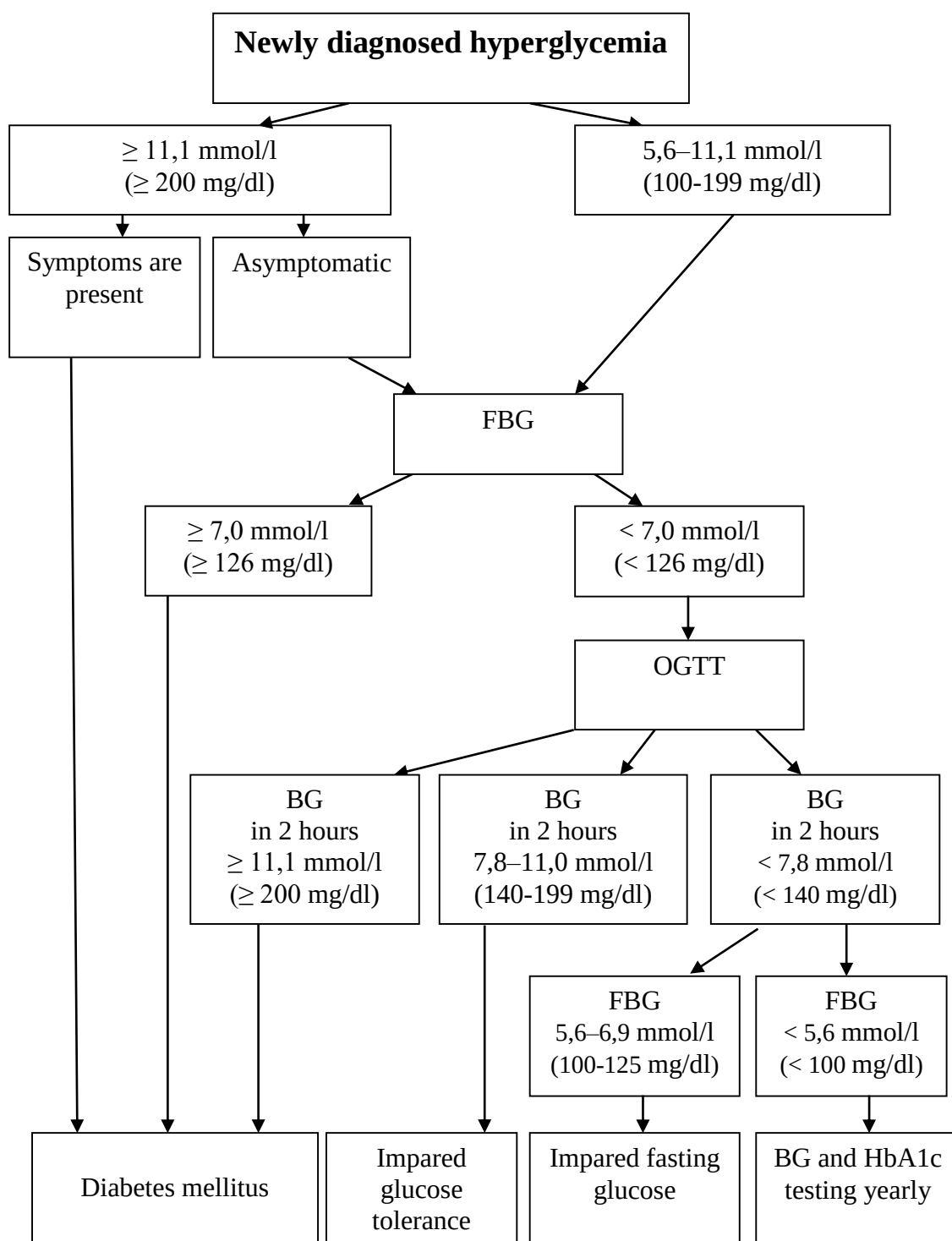
Nowadays the *WHO classification of DM (1999)* is used. It includes the following types of DM.

1. DM type 1 (beta cell dysfunction, corresponding to absolute insulin deficiency):

- A) Immune-mediated;

- C) Idiopathic;

2. DM type 2:



BG – blood glucose, FBG – fasting blood glucose, OGTT – oral glucose tolerance test, HbA1c – glycosylated hemoglobin.

Fig. 1. Management of patients with newly diagnosed hyperglycemia

Stage DM type	Normoglycemia	Hyperglycemia			
	Normal glucose tolerance	Impaired glucose tolerance	DM		
			Relative insulin deficiency		Absolute insulin deficiency
			Does not require insulin	Requires the insulin administration for BG control	Requires insulin administration for survival
DM type 1					
DM type 2					

DM – diabetes mellitus, BG – blood glucose

Fig. 2. Evolution of diabetes mellitus: types of the diseases and clinical stages

2. DM type 2:

- with predominance of IR and relative insulin insufficiency;
- with a predominant violation of insulin secretion with IR;

3. Other specific types of diabetes:

- 1) Genetic defects in β -cells development or function (MODY-1, MODY-9, transient neonatal DM, persistent neonatal DM, mitochondrial DNA mutation and etc.).
- 2) Genetic defects of insulin action (IR type A, leprechaunism, Rabson-Mendenhall syndrome, lipotrophy DM).
- 3) Diseases of an exocrine part of a pancreas (pancreatitis, trauma/pancreatectomy, neoplasms, cystic fibrosis, hemochromatosis, fibrocalculus pancreatopathy, etc.).
- 4) Endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteroma, etc.).

- 5) DM induced by drugs or chemicals (nicotinic acid, glucocorticoids, thyroid hormones, α -adrenomimetics, β -adrenomimetics, β -blockers, thiazides, diazoxide, tyllantine, pentamidine, vacor, α -inter).
 - 6) Infections (congenital rubella, cytomegalovirus, Coxsackie virus, etc.).
 - 7) Unusual immunologically mediated DM (antibodies to insulin, antibodies to insulin receptors, "Stiff-man" syndrome ("rigid man syndrome"), autoimmune polyglandular syndrome type I and type II, IPEX syndrome, etc.).
 - 8) Other genetic syndromes, which are sometimes combined with DM (Down's syndrome, Friedreich's ataxia, Huntington's chorea, Klinefelter's syndrome, Lawrence-Moon-Biddle syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, Turner's syndrome etc.).
4. Gestational DM (GDM) – occurs during pregnancy.

Appropriate diagnostic markers are used to determine the presence of carbohydrate metabolism disorders and its type (Table 2). GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.

Table 2

Diagnostic criteria for DM and other glycemic disorders

	Norm	IGT	DM	IFG
FBG	<5.6 mmol/l (100 mg/dL)	< 7.0 mmol/l (126 mg/dL)	$\geq$ 7.0 mmol/l (126 mg/dL)	5.6 - 6.9 mmol/l (100-125 mg/dL)
OGTT	< 7.8 mmol/l (140 mg/dL)	7.8 - 11.0 mmol/l (140 - 200 mg/dL)	$\geq$ 11.1 mmol/l (200 mg/dL)	< 7.8 mmol/l (140 mg/dL)
HbA1c	< 5.7 %	5.7 - 6.4 %	$\geq$ 6.5 %	< 6.4 %
Additional criteria			Presence of typical DM symptoms, random BG $\geq$ 11.1 mmol/l (200 mg/dl)	

BG – blood glucose, FBG – fasting plasma glucose, OGTT – oral glucose tolerance test, IGT – impaired glucose tolerance, DM – diabetes mellitus, IFG – impaired fasting glucose, HbA1c – glycated hemoglobin.

After a diagnosis of DM has been established the question of a differentiation between its types stands out for the appointment of adequate hypoglycemic therapy. For this purpose investigational plan includes several tests.

1. HbA1c allows to evaluate the average BG level over the last 3 months. Relation between HbA1c and estimated average BG is shown in table 3.

Table 3.

**The relationship between glycated hemoglobin and fasting plasma glucose,
Diabetes Control and Complication Trial (DCCT)**

DCCT formula:

$$\text{eBG in mmol/l} = (1.98 \times \text{HbA1c}) - 4.29$$

$$\text{eBG in mg/dl} = (35.6 \times \text{HbA1c}) - 77.3$$

HbA1c, %		4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1
eBG	mg/dl	65	69	72	76	79	83	86	90	93	97	101	104
	mmol/l	3.6	3.8	4.0	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8
HbA1c, %		5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3
eBG	mg/dl	108	111	115	118	122	126	129	133	136	140	143	147
	mmol/l	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0	8.2
HbA1c, %		6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5
eBG	mg/dl	151	154	158	161	165	168	172	176	180	183	186	190
	mmol/l	8.4	8.6	8.8	9.0	9.2	9.4	9.6	9.8	10.0	10.2	10.4	10.6
HbA1c, %		7.6	7.7	7.8	7.9	8.0	8.5	9.0	9.5	10.0	11.0	12.0	13.0
eBG	mg/dl	193	197	200	204	207	225	243	261	279	314	350	386
	mmol/l	10.8	11.0	11.2	11.4	11.6	12.6	13.5	14.5	15.5	17.5	19.5	21.5

eBG – estimated blood glucose

Adapted from <https://healthy-ojas.com/diabetes/a1c-glucose-chart.html>

2. Insulin-producing function of the pancreas can be evaluated by the measurement of serum C-peptide. C-peptide is a protein that is cleaved from the proinsulin molecule during insulin synthesis. Thus, the amount of circulating in the blood C-peptide is equal to amount of insulin produced by β -cells in the type 1 C-peptide level in blood is low or even undetectable while in DM type 2

C-peptide level may remain within normal limits for a long time or even be elevated (hyperinsulinemia).

3. Using fasting insulin level and FBG measured at the same time HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) can be calculated:

$$\text{HOMA-IR} = \text{FBG (mmol/l)} \times \text{fasting insulin (}\mu\text{U/mL)} / 22.5$$

or

$$\text{HOMA-IR} = \text{FBG (mg/dL)} \times \text{fasting insulin (}\mu\text{U/mL)} / 405.$$

HOMA-IR is used to assess tissue sensitivity to insulin, or insulin resistance. There's no consensus yet, but several studies suggest a cut-off of $\leq 2,5$ for optimal insulin-sensitivity, but normal values appear to vary greatly by population.

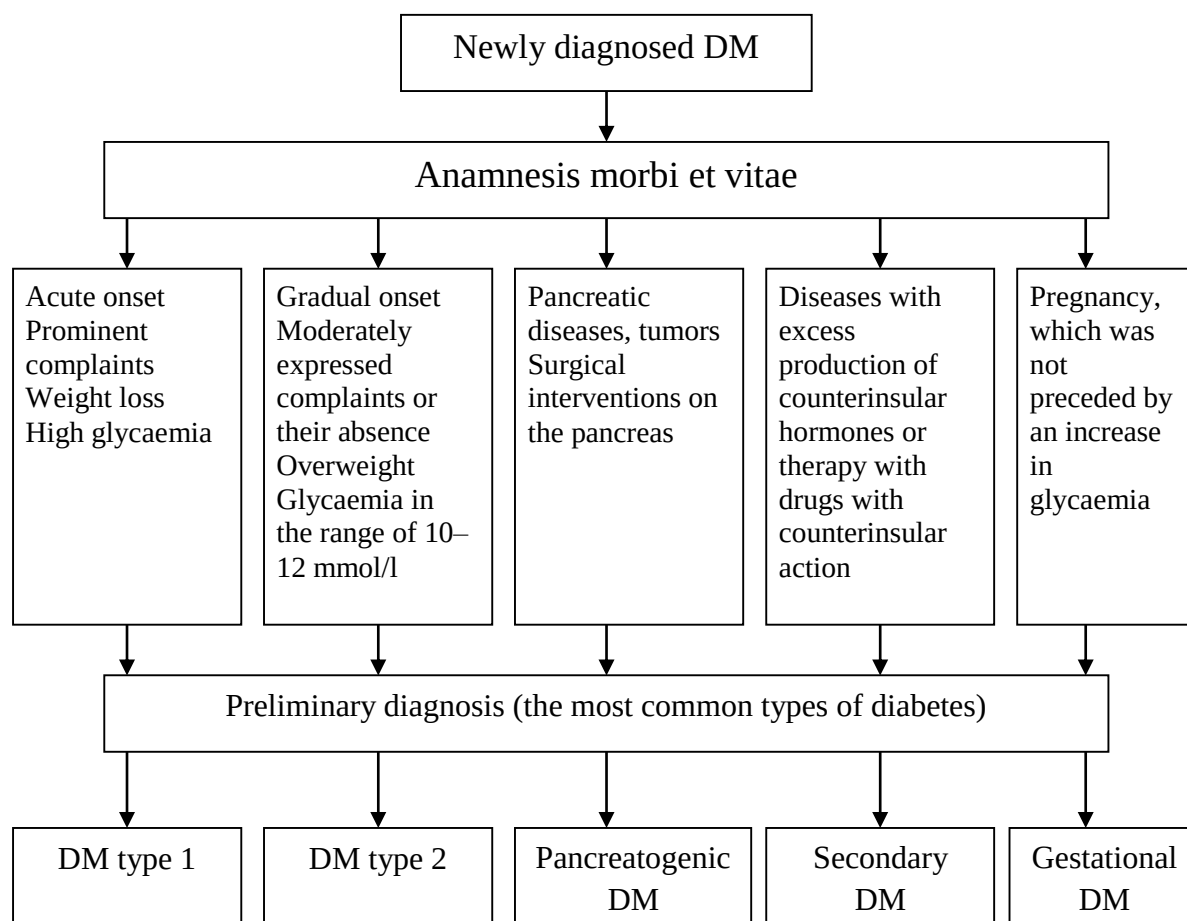
4. Markers of autoimmune β -cells destruction. One of the main causes of β cell dysfunction in DM 1 is their failure as a result of the autoimmune process. The main antibodies that lead to a death of β -cells of the pancreas are: autoantibodies to insulin (IAA), glutamate decarboxylase (GADA), tyrosine phosphatase-like protein (IA-2A), zinc transporter – autoantibodies to ZnT8, island cells autoantibodies (ICA) etc. These autoantibodies are detected in the blood of 85–90 % of patients with DM 1 type. Their presence in the peripheral blood suggests the development of autoimmune insulinitis and confirms type 1 DM.

5. Acetonuria as a laboratory test for ketoacidosis is an evidence of absolute insulin insufficiency. Normally ketone bodies (***beta-oxybutyric and acetoacetic acids, acetone***) are contained in urine in extremely small concentrations. Their increase occurs proportionally to the level of glycaemia and insulin deficiency. As a result of absolute insulin insufficiency there is an increase in the production of ketone bodies from triglycerides and at the same time decrease in their utilization in the liver. The presence of ketonuria is an indicator of DM decompensation.

6. Fructosamine assay allows to evaluate the average level of glycaemia over the preceding 3 weeks, but this test has limited use in practice.

2.5. Differential diagnosis of DM types

Thorough interviewing allows to assume a particular type of DM in a patient (Fig. 3).



DM – diabetes mellitus

Fig. 3. Algorithmic approach to the preliminary diagnosis of diabetes mellitus type based on the anamnesis

In vast majority cases the diagnosis of DM type 1 is unquestionable because of acute onset and typical prominent clinical picture. The disease develops acutely, most common after stress or severe illness, in particular after viral illness. Besides pronounced «diabetic» complaints (polyuria, polydipsia, dry mouth), patients report general weakness, weight loss despite increased appetite. DM type 1 manifestation commonly occurs «under the mask» of acute abdomen so the challenge for the physician in such cases lies in thorough evaluation of a patient

to avoid unnecessary surgical intervention. The smell of acetone is often felt to the patient's breath. The BG, as a rule, significantly exceeds 10 mmol/l, sometimes reaching 30 mmol/l. Because in the conditions of absolute insulin insufficiency an organism is compelled to rely on protein and fat catabolism for energy. Free fatty acids become the main energy substrate for all tissues except the brain. Body mass is decreased and ketonuria occurs. Ketone bodies are toxic to the brain, so their presence in patient's blood for some time can cause central nervous system disorders, ranging from a slow response to questions up to loss of consciousness and developed coma. The above, as a rule, is enough to make a diagnosis of a DM 1 type.

Reduced level of serum C-peptide is an additional confirmation of absolute insulin deficiency and positive titers of antibodies to structural proteins of islet cells of the pancreas indicate the autoimmune nature of type 1 diabetes. Type 1 diabetes is often combined with other autoimmune diseases (eg, autoimmune thyroiditis, vitiligo, primary adrenal insufficiency, etc.). In vast majority cases, DM type 1 develops in children and young people, but age is not a diagnostic criterion of DM type 1, which may manifests even in the elderly.

Unlike DM type 1, DM type 2 has torpid development, often from the moment of disease manifestation to the diagnosis several years passed. «Diabetic» complaints in DM type 2 are moderate, and sometimes are absent because of patient's adaptation to hyperglycemia. Gynecologists often diagnose DM in women, as vaginal itching is often the only complain. In addition, DM type 2 can be diagnosed by doctors of other specialties, as it cause atypical complains, such as pain, numbness in the extremities, decreased visual acuity, heart pain, periodontitis and others. FBG rear exceeds 10–12 mmol/l, acetonuria is not observed due to sufficient reserves of glycogen in the absence of insulin deficiency – DM type 2 is characterized by relative insulin deficiency. Relative insulin deficiency is a mismatch between beta cells ability to synthesize insulin and its needs in conditions of reduced tissue sensitivity to insulin – IR. C-peptide

is normal or elevated due to sufficient or excessive (over some time) insulin secretion by beta cells to overcome IR. IR is evaluated by HOMA-IR index (> 2.5).

There are also some special types of DM, among which the most common is a latent autoimmune diabetes of adults (LADA), which has clinical signs of both DM type 1 and DM type 2. As a rule, LADA manifests as DM type 2 but the progression of the disease from the stage of relative insulin deficiency, when oral hypoglycemic therapy is effective, to absolute insulin insufficiency occurs fairly quickly – no longer than 5 years. During the first years from the beginning of a disease autoimmune markers of islet cells damage are found. Thus, the presence of DM of this type can be assumed, as a rule, only a few years after the onset of the disease.

The so-called symptomatic diabetes can be suspected if the patient has comorbid pathology accompanied by excessive production of counterinsular hormones, or a history of treatment with drugs that have counterinsular effects (see op. 3 of the DM classification). The disease has signs of DM type 2 but the relative insulin deficiency in this case is not due to a decrease in insulin production and violation of its action on the background of IR.

Pancreatic diseases in an anamnesis such as chronic pancreatitis, pancreatic necrosis, tumors, etc., especially on the background of alcohol abuse or pancreatic surgery suggest the presence of so-called pancreatogenic diabetes (see p. 3 of the DM classification). This type of DM is accompanied by primary insulin dependence due to absolute insulin deficiency, but is not a type of DM type 1 which has a completely different nature. In pancreatogenic diabetes endogenous insulin deficiency is associated with mechanical damage to the islet apparatus (eg, pancreatitis), infections (pancreatic necrosis), neoplastic transformation, surgical removal or traumatic damage of a part of a pancreas. Previously diagnosed and documented pancreatic diseases or results of appropriate instrumental, imagine etc. studies will support a diagnosis of pancreatogenic DM.

GDM as it was mentioned above is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It should be noted that pregnancy can occur on the background of type 1 or type 2 DM. In these cases DM in pregnant women is regarded not as gestational, but as type 1 or type 2, respectively. In addition, approximately 6 weeks after delivery, a woman with GDM should be reclassified and assigned to one of the following categories: DM, IFG, IGT, normoglycemia.

3. TREATMENT OF DM DEPENDING ON ITS TYPE

Because DM is a dangerous disease due to the many complications caused by hyperglycemia, the aim of its treatment is to reduce all glycemic parameters to values as close as possible to the target ones.

The goals of glycemic control should be individual depending on age, life expectancy, presence and severity of complications, etc. For example, in an elderly patient with DM who is treated with insulin and has severe comorbid cardiac pathology, it should not strive to achieve normoglycemia because it increases the risk of hypoglycemic reactions with subsequent cardiovascular events (myocardial infarction, acute cerebrovascular accident) and possible fatal consequences. In addition in patients with asymptomatic HypoGl a higher level of glycemia is allowed as a treatment goal.

Treatment of DM involves control of carbohydrate metabolism + correction of lipid disorders + correction of hypertension. Achieving compensation for only one or two of these parameters does not reduce the risk of developing and progressing late complications of DM. The targets for carbohydrate metabolism compensation in DM, according to the recommendations of the ADA, 2023, are as following:

- FBG 4.4–7.2 mmol / l (80–130 mg / dL);
- Postprandial BG < 10.0 mmol / l (<180 mg / dL);
- HbA1c <7.0 % (<53 mmol / mol).

Management of DM includes diet, physical activity, patient education the methods and basic principles of self-control and the use of glucose lowering medications. The first three methods practically do not differ in patients with different types of DM, however, the use of hypoglycemic agents has its own rules and differences.

3.1 Pharmacologic therapy of DM type 1

Since type 1 diabetes is a consequence of the destruction of the insulin-producing apparatus of the pancreas, the only method of its treatment is insulin replacement therapy (IT), the main goal of which is to maintain a state of carbohydrate metabolism close to that of a healthy person. Ideal IT mimics endogenous insulin secretion. For this purpose, a base-bolus (or intensified) scheme using short-acting insulins (or ultra-short-acting insulin analogues) in combination with intermediate-acting insulins (or long-acting insulin analogues) is used. Short-term insulins are administered depending on food intake, and long-term insulins have a fixed time of administration that does not depend on the food load.

Insulin analogues, due to the changed chemical structure, fully achieve the goal of IT (simulation of natural secretion of a pancreas). Ultra-short-acting insulin analogues quickly «quench» the postprandial increase in BG, and ultra-long-acting insulin create a flat plateau of the basic insulin concentration in the blood. Due to its mechanism of action, prandial insulin can be administered immediately before a meal, during a meal, or even after it, and ultra-long-acting insulins have practically no concentration peaks, which, with a correctly set dose, minimizes the likelihood of HypoGl. The basic scheme of ideal insulin replacement strategy is as follows (Fig. 4):

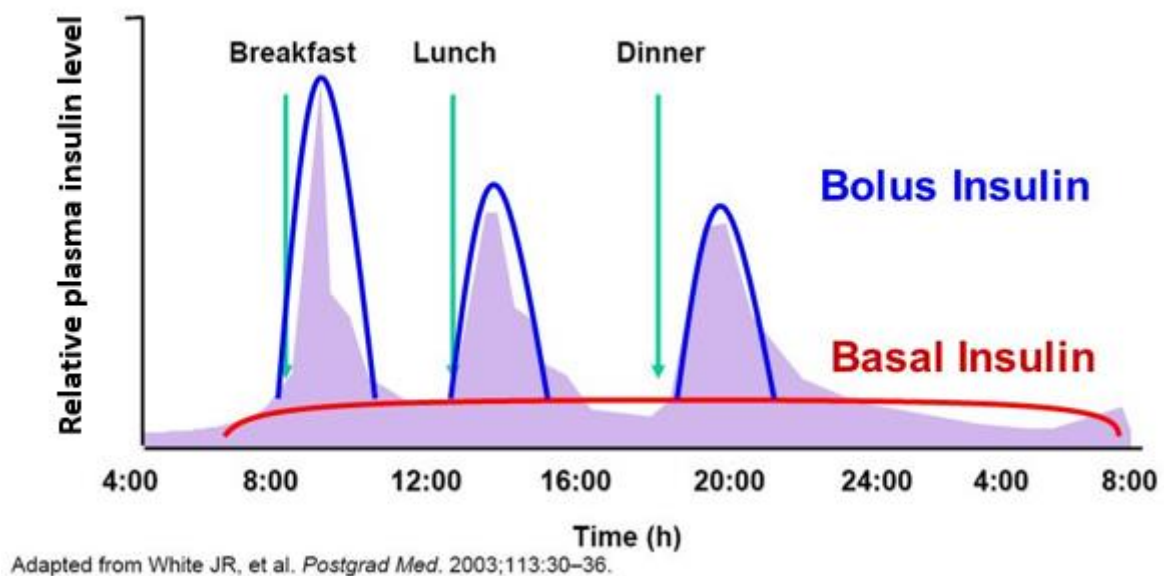


Fig. 4. The basic scheme of ideal insulin replacement strategy

Fig. 5 represents insulin categorization by how fast it works in the body, how soon it peaks and then how long it lasts. Thus, short-acting insulin controls postprandial blood glucose levels, and long-acting insulin controls the period between meals and at night.

Rapid-acting (ultra-short-acting) insulins are used whenever a rapid onset and short duration are appropriate (eg, before meals or when the blood glucose level exceeds target and a correction dose is needed). Rapid-acting insulins are associated with less HypoGI than regular insulin.

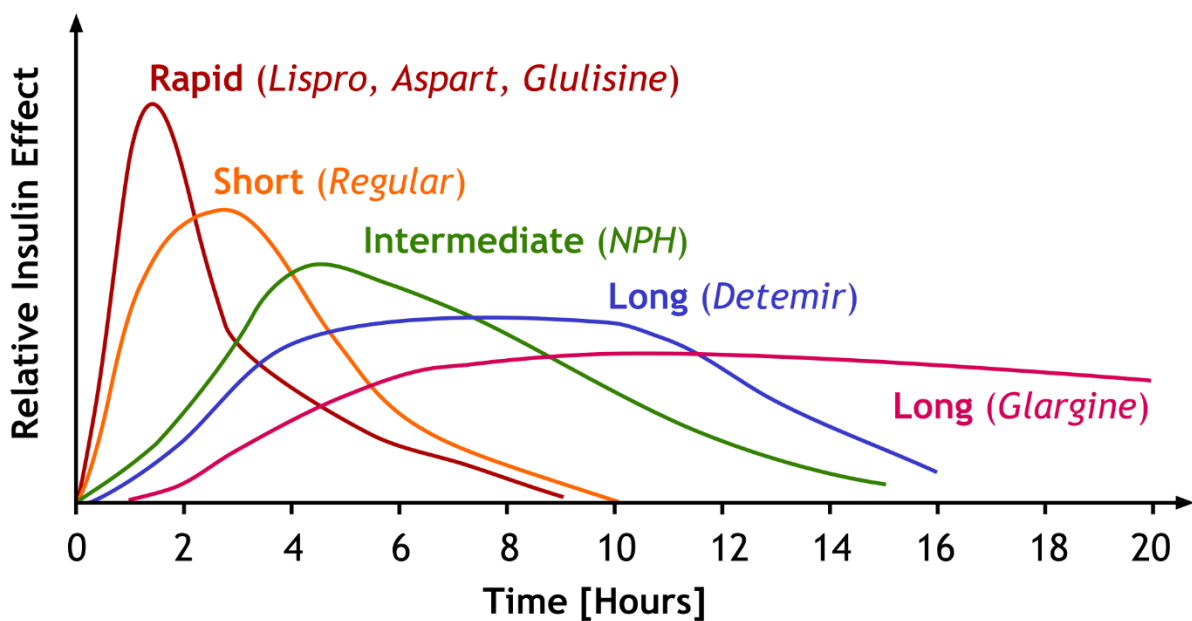
Currently, short-acting insulins are less commonly used than the rapid-acting insulins in patients with type 1 DM. They are used when a slightly slower onset of action or a greater duration of action is desired.

Intermediate-acting insulins have a relatively slow onset of action and a relatively long duration of action. They are usually combined with faster-acting insulins to maximize the benefits of a single injection.

Long-acting and ultralong-acting insulins have a very long duration of action and, when combined with faster-acting insulins, provide better glucose control for

some patients. In patients with type 1 DM, they must be used in conjunction with a rapid-acting or short-acting insulin given before meals.

Premixed insulins contain a fixed ratio of rapid-acting insulins with longer-acting insulin, which can restrict their use. Premixed insulin is usually not recommended in type 1 DM patients, because of their need for frequent adjustments of premeal insulin doses.



<https://www.grepmed.com/images/1768/endocrinology-pharmacology-half-life-duration-diabetes>

Fig. 5. Insulin categorization by its time of action

Methods of insulin dose adjustment are divided into retrospective and prospective. In the retrospective method insulin is administrated taking into account the previous dose and glycemic parameters, and in the prospective method insulin is prescribed for the first time empirically. The initial daily insulin dose in an adult is usually 0.5–1 U/kg. The dose for children can be higher – up to 2 U/kg, and in pregnant women it depends on the gestational period: about 0.7 U/kg/day in the first trimester, 0.9–1.2 U/kg/day in the second and third trimesters, with a decrease in insulin dose until delivery to 0.7–0.8 U/kg/day.

If insulin dose is calculating taking into account the duration of the disease, the average daily dose of insulin in the 1st year is 0.5 U/kg/day, in the following

years – 0.7 U/kg/day, in patients with high physical activity – 0.5 U/kg/day, sedentary lifestyle - 0.7 U/kg/day, in stress periods – 1.0 U/kg/day, during puberty – 1.0–2.0 U/kg/day, ketoacidosis, treatment with glucocorticoids – up to 1.5–2 U/kg/day.

The daily dose of insulin is divided into 4–5 subcutaneous injections (three times before the main meals short-acting or ultra-short-acting insulin and twice or once intermediate-acting or prolonged-acting insulin, respectively). The proportion of prolonged insulin to simulate the basic secretion of insulin is about 50 %. Insulin dose adjustment is based on daily glycaemia self-control data and amount of carbohydrates in the meal, up to achievement of individual targets of a carbohydrate metabolism parameters. The increase in total insulin dose by more than 8 U per day (or 2–3 U per administration) is not recommended.

The optimal time for short-acting insulin administration is 20-30 minutes before a meal, ultra-short - immediately before, during or even after a meal, due to the special properties of its pharmacokinetics. It is advisable to refrain from the simultaneous introduction of more than 12 units of short-acting insulin, because, firstly, this significantly increases the risk of HypoGI and related complications, and secondly, there are data that more than 12 units of insulin cannot bind with insulin receptors and circulates in the blood, causing the formation of anti-insulin antibodies. The most convenient is the use of insulin analogs, because they have a physiological profile of action and allow better glycemic control with a lower risk of HypoGI and weight gain.

Insulin can be administered using insulin syringes (at the same time, it is important that the concentration on the vial of insulin coincides with the concentration on the syringe, for example, 100 units/ml), ready-to-use syringe pens (pre-filled with insulin) or with replaceable cartridges, and with using insulin pumps –devices for continuous subcutaneous infusion of insulin, including with constant monitoring of glucose levels. In the latter case, only ultra-short-acting insulin analogs are used. Currently, inhalers for insulin inhalation are being

developed. However, the question of the exact dosage of the drug has not yet been fully resolved.

IT side effects:

- HypoGl;
- lipotrophy or lipohypertrophy at injection sites;
- local allergic reactions (generalized allergy – rare);
- peripheral edema;
- impaired vision.

Most of them can be avoided by correctly calculating the required doses of insulin and following the rules for performing injections.

Against the background of IT morning hyperglycemia, *not associated with an insufficient dose of evening prolonged insulin*, may occur:

1. The Somogyi phenomenon is a posthypoglycemic hyperglycemia. This phenomenon occurs with an overdose of the evening dose of long-acting insulin, when HypoGl develops between 2 and 4 a.m. (clinically it is manifested by nightmares, unconscious actions in a dream, morning headache and feeling unwell, under the weather) due to the fact that the maximum insulin effect coincides with the period of lowest counterinsular hormones level at the background of maximal tissue insulin sensitivity (see image 1). The development of HypoGl at this time causes a significant compensatory release of glucagon and other counterinsular hormones, followed by hyperglycemia in the morning hours. In this case, the treatment tactics include reducing the evening dose of prolonged insulin or rescheduling the injection to 10 p.m. in case of insulin administration at an earlier time.

2. The dawn phenomenon - is an abnormal early morning increase in the blood glucose level because of natural changes in hormone levels. It is due to an increase in the need for insulin in the morning hours, when the process of waking up includes a change in the biorhythm of the secretion of counterinsular hormones, which increase BG level. In a healthy person, in response to this, insulin is

released, which prevents the development of hyperglycemia until the moment of awakening, since there is enough insulin in the body to compensate for the counterinsular action of «hormones of the dawn». In this case, the only way to avoid morning hyperglycemia is to inject a small dose of short-acting insulin (usually 2–4 U) in the early morning hours (5.00-6.00) without a meal.

It should be kept in mind the possibility of remission of DM type 1, so-called «honeymoon phase», which is manifested in a decrease in the need for exogenous insulin shortly after the manifestation of the disease and the beginning of IT with a dose $\leq 0.3\text{--}0.4$ U/kg (sometimes the daily dose may be 2–4 U of prolonged insulin per day). The duration of this period can be from several months to several years, when the final autoimmune destruction of beta cells, which still remained functional, occurs. Tactics of treatment in the honeymoon phase DM: complete cancellation of IT is not allowed, even under conditions of normalization of BG. IT is carried out according to the needs of the patient with regular monitoring of the carbohydrate metabolism state (BG during the day, HbA1c once every 3 months) in order to prevent a sharp decompensation of DM after the end of honeymoon period.

3.2 Pharmacologic therapy of DM type 2

If lifestyle changes are ineffective (diet, physical activity, weight loss) for 3 months, the patient must be additionally prescribed glucose lowering therapy (GLT).

Glucose lowering drug (GLD) classes used for the treatment of DM type 2 include the following:

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)

- Glucagonlike peptide-1 (GLP-1) agonists
- Dual GLP-1 and glucose-dependent insulinotropic polypeptide agonists
- Dipeptidyl peptidase IV (DPP-4) inhibitors
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
- Insulins

Classification of GLD by mechanism of action:

- Drugs that increase insulin secretion (secretagogues): sulfonylureas, meglitinide, GLP-1 agonists, DPP-4 inhibitors.
- Drugs that increase the sensitivity of peripheral tissues to insulin (sensitizers): TZDs, biguanides.
- Drugs that reduce glucose production in the liver.
- Drugs that reduce the absorption of carbohydrates in the intestine: α -glucosidase inhibitors.
- Drugs that promote the excretion of excess glucose in the urine - SGLT-2 inhibitors.

According to international and local management protocols for patients with DM type 2, biguanides (metformin), which affect IR and do not have a direct stimulating effect on the pancreas (i.e. not a hypoglycemic but an antihyperglycemic drug), have been the first-line drug for many years. It is prescribed at a dose of up to 2000 mg/day from 1 to 3 doses during or after meals. There are long-acting metformin drugs that are prescribed once, usually in the evening, and have fewer side effects. If after 3 months of therapy with the maximum doses of metformin, compensation of carbohydrate metabolism has not been achieved, combined therapy is indicated. The combined GLT is performed in accordance with a Consensus Report by the ADA and the

European Association for the Study of Diabetes (2022) and is based on a patient-oriented approach, taking into account the presence or absence of atherosclerosis and chronic kidney disease (taking into account contraindications and, on the contrary, evidence of a positive effect of certain GLD on the cardiovascular and urinary systems). The monitoring of GLT efficacy is carried out once every 3 months by HbA1c level assessment. At the stage of GLT intensification, any GLD can be added to metformin, including insulin (Fig. 6).

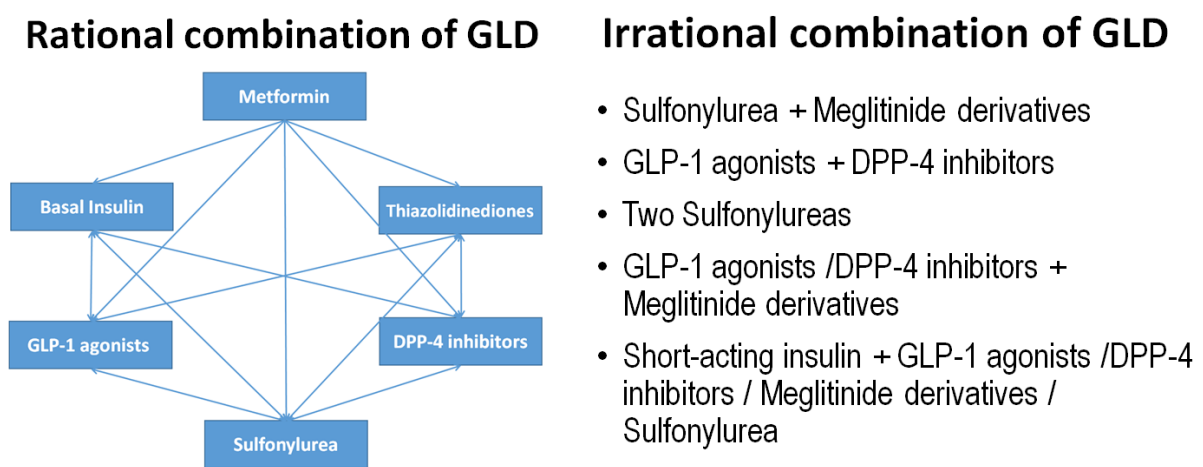


Fig. 6. Combinations of glucose lowering drugs

Each group of GLDs has its advantages, disadvantages and features of application. From a practical standpoint the most important are the following:

- The most common side effect of metformin affects bowel motor function in the form of diarrhea and/or nausea. If this phenomenon does not disappear within several days, the dose should be reduced. Metformin should be cancelled if symptoms does not disappear at the minimum dose (500 mg/day). In this case a GLD from the other group must be prescribed.
- Secretagogues as well as insulin can cause HypoGl.
- The use of sulfonyleureas is justified only in patients with DM type 2 with preserved beta-cell secretion; long-term use of these drugs causes beta-cell depletion, accompanied by deterioration of diabetes compensation.

- GLP-1 agonists and DPP-4 inhibitors due to their mechanisms of action improve glucose-dependent insulin secretion and reduce increased glucose secretion, i.e. have a physiological mechanism of action on insulin-producing function of the pancreas.
- The effect of SGLT-2 inhibitors does not depend on the patient glycemic status and reduce renal glucose reabsorption with subsequent reduction of hyperglycemia, renal excretion of glucose and decrease in body weight. Inhibition of sodium-glucose transport is accompanied by a weak diuretic and transient natriuretic effect. Due to the mechanism of action, this drug can be added to any previous GLT.
- The peculiarity of IT in DM type 2 is the possibility of mixed insulins use with a fixed combination of components, taking into account the final secretion of insulin by the pancreas.
- A combination of GLP-1 agonist lixisenatide and long-acting insulin glargine (brand name – Soliqua) or GLP-1 agonist liraglutide and long-acting insulin degludec (brand name – Xultophy) can be used.

Given the spontaneous evolution of type 2 DM, which eventually transforms the relative insulin deficiency into absolute insulin deficiency, IT at some stage becomes necessary to maintain carbohydrate metabolism compensation and/or to ensure the viability of patients with type 2 DM. Other indications for IT in patients with DM type 2 are the next:

- in persons with the first known DM type 2 at the level of HbA1c > 9 % and the presence of severe clinical decompensation (a temporary prescription of IT is possible);
- in the presence of contraindications or intolerance to the other GLD;
- in ketoacidosis;

- in case of surgery, acute concomitant illness and exacerbations of chronic intercurrent diseases, which accompanied with carbohydrate metabolism decompensation (temporary IT).

3.3 Treatment of pancreatogenic DM

Given the mechanism of development of this type of diabetes, the only method of GLT in this case is IT, which carried out according to the principles of DM type 1 treatment.

3.4 Treatment of symptomatic DM

The pathophysiology of this type of DM is associated with excessive action of endogenous or exogenous counterinsular hormones with normal or increased insulin secretion. Thus, treatment involves eliminating of provoking factors (if possible) and prescribing drugs that ensure the effect of endogenous insulin and eliminate IR (sensitizers).

If the effect of provoking factors is too long, over time the functional state of the insulin-producing apparatus of the pancreas is disrupted and the need for intensification of therapy is required, which is based on the principles of DM type 2 treatment.

3.5 Treatment of DM during pregnancy

For GDM use lifestyle changes and/or IT. Type 1 DM continue to treat with insulin. In DM type 2 that requires GLT, oral agents are discontinued because they penetrate through the placental barrier, and IT is assigned according to the generally accepted scheme.

4. MANAGEMENT OF PATIENTS WITH HYPOGLYCAEMIC STATES

Most researchers define hypoglycemia (Greek *hypo* – low + *glykys* – sweet + *haima* – blood) as a symptom complex of vegetative, neurological and psychiatric disorders observed when the concentration of glucose in the blood drops up to 3.5 mmol/l. There are evidences of sex differences in BG levels, when the hypoglycemic state defined a decrease in BG below 2.5–2.8 mmol/l in men and below 1.9–2.2 mmol/l in women. But there is no the only generally accepted definition of HypoGl, as well as the BG level that corresponds to HypoGl.

It should be noted that independently of the chosen HypoGl criterion when assessing this condition, one should take into account the absence of a strict correlation between the level of BG and clinical symptoms of HypoGl. That is, HypoGl is more clinical concept than laboratory, and its symptoms disappear after BG normalization.

In patients with DM symptoms of a hypoglycemic state are observed at significantly higher BG values than in healthy individuals, which is due, firstly, to the body's «getting used to» much higher than normal values of BG, and secondly, to a rapid drop of BG at the background of GLT (primarily, insulin).

Classification of hypoglycemic states according to the conditions of HypoGl development:

1. on an empty stomach;
2. after eating (alimentary) - develops 1.5-3 hours after a meal. The causes of alimentary HypoGl are rapid emptying of the stomach and intestines due to surgical interventions (resection of the part of the stomach or gastrectomy, anastomosis of the stomach and small intestine, plastic surgery of the pyloric part of the stomach, vagotomy), early phase of DM, use of products with fructose in children with impaired tolerance to fructose, use of galactose in children with galactosemia;

3. after exercise (when glucose is used up, and easily digestible carbohydrates do not enter the body).

Classification of hypoglycemic states by etiology:

1. HypoGl in children (60 %)

1) In newborns:

- a) deficiency of glucose or its sources (in premature infants, in premature infants with low weight, in the smaller of the twins, in newborns from mothers with preeclampsia);
- b) hyperinsulinemia (DM in the mother, hemolytic disease of newborns).

2) In children of any age:

a) hyperinsulinemia:

- nesidioblastosis (syn. neonatal hypoglycemic syndrome, hyperinsulinemic HypoGl of newborns, congenital hyperinsulinism) - a congenital condition manifested by the ability of acinar cells to transform into beta cells;
- congenital beta-cell hyperplasia (idiopathic neonatal hypoglycaemia);
- tumors of the insular apparatus (insulinomas);
- Beckwith-Wiedemann syndrome (rare genetic abnormality, including, among others, hyperplasia of the islet apparatus of the pancreas);

b) deficiency of counterinsular hormones (panhypopituitary syndrome, isolated somatotropin deficiency, isolated ACTH deficiency, primary adrenal insufficiency, congenital conditions manifested by glucagon and adrenaline deficiency);

c) deficiency of glucose or its sources:

- fasting HypoGl;
- leucinos (maple syrup urine disease) - congenital enzymopathy;

d) glycogenosis I, III, VI types (lack of enzymes required for normal glucose metabolism);

e) glycogen synthetase deficiency;

- f) violation of gluconeogenesis (deficiency of fructosediphosphatase and other enzymes);
- j) galactosemia;
- h) fructose intolerance;
- g) alcoholic HypoGl;
- i) drug induced HypoGl (insulin overdose).

2. HypoGl in adults:

- a) hungry HypoGl (starvation, deficiency of carbohydrate-containing products);
- b) iatrogenic HypoGl (insulin overdose, overdose or hypersensitivity to oral hypoglycemic agents; use of salicylates (indomethacin), chloramphenicol, tetracycline, haloperidol, beta-blockers, barbiturates, antihistamines, anticoagulants of indirect action, paraaminosalicylic acid, monoamine oxidase inhibitors, magnesium-containing drugs, clonidine, clofibrate, etc.);
- c) alcoholic HypoGl;
- d) insulinoma;
- e) tumors that do not contain beta cells (mesothelioma, fibrosarcomas, lymphomas, adrenal cancer, hepatocellular carcinoma, neurofibroma).

In order to confirm HypoGl, the presence of the so-called *Whipple's triad* is required:

1. the attack develops after a long break after eating or after exercise;
2. glucose levels have been documented to be below 2,78 mmol/l (50 mg/dL);
3. improvement of the patient's condition occurs after oral or parenteral administration of glucose (increased glycemia).

HypoGl clinical presentation, regardless of its causes, has two groups of symptoms:

1. Adrenergic diseases associated with activation of the autonomic nervous system (general weakness, sweating, palpitations, tremors, irritability, tingling of

the lips and fingers, hunger, etc.). These symptoms are precursors of the HypoGl. They can develop even at a normal level of BG under conditions of its sharp fall.

2. Neurological symptoms - disorders of the central nervous system in true HypoGl (headache, decreased body temperature, visual disturbances, dizziness, amnesia, convulsions, loss of consciousness, coma).

Manifestations of HypoGl depend on concomitant pathology, the state of the endocrine system, patient phenotype, the type of mental activity, upbringing and educational level. Obesity often develops due to excessive intake of refined carbohydrates in common HypoGl (as a result of a GLD overdose).

According to the severity HypoGl is broken down into:

- mild, that patients can overcome on their own;
- moderate, that is overcome by oral administration of glucose, however, at the same time, the help of outsiders is needed due to the development of moderate disturbances of consciousness in the patient (confusion, inappropriate behavior, excitement, etc.);
- severe, with complete patient disorientation, loss of consciousness, requires urgent emergency treatment (glucose, glucagon, etc.).

Asymptomatic hypoglycemia is also distinguished, which includes episodes of a decrease in the level of BG below 3.9 mmol/l in the absence of any clinical manifestations of this condition. In contrast to the above, the development of a hypoglycemic symptomcomplex, which is not confirmed by the results of the BG measurement, is considered probable HypoGl.

ADA (2023) recommends next definition of HypoGl levels:

Level	Glycemic criteria	Description
Level 1 – HypoGl of alarming value	< 3.9 mmol/l (70 mg/dL) and ≥3.0 mmol/l (54 mg/dL)	Glycemia is low enough to treat fast-acting carbohydrates and adjust the dose of GLD
Level 2 – Clinically significant HypoGl	<3.0 mmol/l (54 mg dL)	Sufficiently low BG levels for the diagnosis of clinically significant HypoGl
Level 3 – Severe HypoGl	There is no special glucose threshold	HypoGl, associated with severe cognitive impairment, requiring assistance

BG – blood glucose, GLD – glucose lowering drug, HypoGl – hypoglycemia.

Adapted from American Diabetes Association; 6. Glycemic Targets: *Standards of Care in Diabetes—2023*. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S97–S110. <https://doi.org/10.2337/dc23-S006>

Hypoglycemic state cannot last long. There are two possible outcomes: recovery to normoglycemia due to endogenous or exogenous factors or coma.

Diagnosis of a hypoglycemic state does not cause difficulties, as it is based on the characteristic clinical picture and the results of BG measurement at the time of the attack. In addition, emergency care for HypoGl does not depend on its cause. The goal of treatment includes correcting the glucose deficit, preventing the development of complications associated with HypoGl, and treating the cause of the underlying condition.

The HypoGl management algorithm is shown in fig. 7.

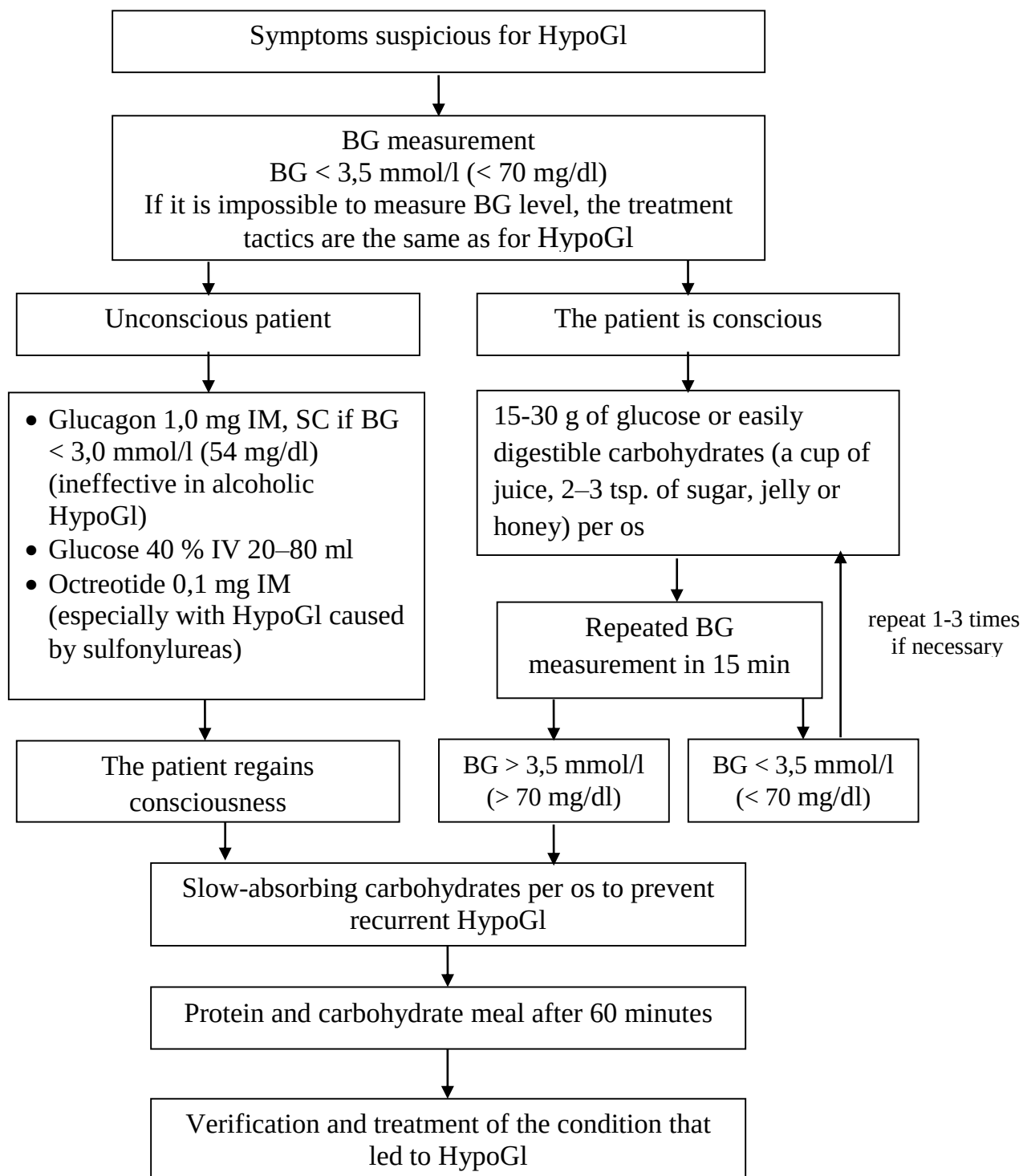
Clarification of the mechanism that led to the development of HypoGl (that is, establishing the primary diagnosis) will make it possible to prescribe pathogenetic therapy and minimize the possibility of hypoglycemic states in the future.

Let's consider the most common causes of HypoGl in adults and the management of patients in these cases.

1. The so-called «hungry» HypoGl needs correction of the dietary regimen (consumption of hard-to-digest carbohydrates).
2. Tactics for the drug-induced HypoGl means withdrawal or correction of the dose of the drugs that caused it. Most often, the cause of drug-induced HypoGl in

patients with a history of DM is inadequate prescription of GLT or non-compliance with the regimen by the patient. If there is an overdose of insulin, dose correction is carried out in accordance with the mechanism of its action. For example, if HypoGI occurs 2–3 hours after the introduction of short-acting insulin (that is, at the peak of effectiveness), there is an overdose of this insulin and its dose should be reduced. If hypoG is observed at night (may manifests with sweating, nightmares, waking up because of hunger, etc.), patients need to reduce the evening dose of long-acting insulin. Clinically significant HypoGI caused by oral GLD (most often, sulfonylureas) is not so common, but they are more complicated, since modern drugs mostly have a daily duration of action. In this regard, patients need frequent intake of carbohydrates for a long time, sufficient to reduce the concentration of the drug in blood (about a day). Further patient needs a dose correction or a change of the GLT scheme.

3. Alcoholic HypoGI is treated symptomatically, and alcohol cessation is recommended.



BG – blood glucose, HypoGl – hypoglycemia, IM – intramuscular, SC – subcutaneous

Fig. 7. Hypoglycemia management algorithm

4. Insulinoma (or hypoglycemic disease) is characterized by absolute endogenous hyperinsulinism due to increased production of insulin by pancreatic beta cells.

Diagnostic criteria of insulinoma:

- HypoGI symptoms ;
- BG <3.0 mmol/L (<55 mg/dL);
- serum insulin $\geq 3 \mu\text{U/ml}$ ($\geq 18 \text{ pmol/l}$);
- serum C-peptide $\geq 0.6 \text{ ng/ml}$ ($\geq 0.2 \text{ nmol/l}$);
- serum proinsulin $\geq 5.0 \text{ pmol/l}$.

Topographic diagnosis is reduced to contrast-enhanced computed tomography or magnetic resonance imaging. These methods allow detecting insulinoma in 70–80 % of cases, since in 90 % of cases the tumor is small in size (< 2 cm in diameter).

To confirm endogenous hyperinsulinism in doubtful cases fasting test is carried out. A patient does not eat for 72 hours. BG and blood insulin are determined before the test. Glycemia is assessed every 2-4 hours. If the patient develops documented hypoGI within 72 hours, repeated blood insulin level determined and the test is stopped. Not only the level of the hormone itself (which increases with insulinoma), but also the ratio of insulin (pmol/l) to BG (mmol/l) are evaluated. If this ratio exceeds 37 in any of the samples, this confirms the diagnosis of insulinoma.

Insulinoma treatment is surgical. In situations when the tumor is inoperable or not detected by imaging methods, drugs that suppress insulin secretion are used to alleviate the condition:

- 1) diazoxide 100 mg per os 3–4 times per day (peripheral vasodilator, which has the effect of blocking insulin production);
- 2) octreotide 0.1 mg s/c 1–5 times a day (synthetic analogue of somatostatin, which inhibits insulin secretion by binding to somatostatin receptors).

Insulinoma must be differentiated from reactive HypoGI (see table 4).

Table 4

Insulinoma differential diagnosis clues

	Insulinoma	Reactive HypoCl
Conditions of HypoCl occurrence	More often on an empty stomach, during breaks between meals and after exercise	Against the background of physical exertion, with episodic food intake, not balanced in terms of carbohydrates. The provoking factor is premenstrual syndrome «Hungry Fainting»
HypoGl trigger (provoking test)	Fasting (fasting test)	Intake of large amounts of refined carbohydrates (OGTT)
Cause	Hyperproduction of insulin by the tumor	Glycogen deficiency (decrease in glycogen stores in the liver against the background of glucose deficiency)
Clinical features	Predominantly neurological symptoms (visual disturbances, transient neurological disturbances, seizures, personality changes), overweight/obesity as a result of overeating to stop the hypoglycemic reaction	Sympatho-adrenal symptoms are in the foreground
Treatment	Surgical or supportive (if it is impossible to carry out surgical intervention)	Recommendations: • Diet with a restriction of moncarbohydrates, 30-40% of calories due to difficult to digest carbohydrates, with high protein and fat content. • Long breaks between meals are not allowed.

HypoGl – hypoglycemia, OGTT – oral glucose tolerance test

5. Counterinsular hormones deficiency in case of hypopituitary syndrome (STH, ACTH deficiency), primary adrenal insufficiency prevention of hypoglycemic states is reduced to compensation of the corresponding hormonal shift by adequate doses of hormone replacement therapy (with growth hormone preparations for somatotrophic insufficiency, glucocorticoids for adrenal insufficiency).

SELF-ASSESSMENT. MCQs

1. What of the following is the drug of choice for the initial treatment of type 2 DM?
 - a) glimepiride,
 - b) metformin,
 - c) pioglitazone,
 - d) insulin,
 - e) gliclazide.
2. When a patient with DM type 2 requires mandatory insulin therapy?
 - a) in the absence of compensation of carbohydrate metabolism against the background of diet and phytotherapy,
 - b) in the absence of compensation of carbohydrate metabolism against the background of metformin treatment in the maximum dose,
 - c) when changing time zones,
 - d) in case of mild acute respiratory viral infection against the background of compensation of carbohydrate metabolism by oral GLT,
 - e) in case of cavity surgery.
3. What level of fasting blood glucose indicates the presence of DM in a patient?
 - a) $> 5.5 \text{ mmol / l}$,
 - b) $5.6\text{-}6.9 \text{ mmol / l}$,
 - c) $\geq 7.0 \text{ mmol / l}$,
 - d) $\geq 7.8 \text{ mmol / l}$,
 - e) $\geq 11.1 \text{ mmol / l}$.
4. What does the level of HbA1c indicates?
 - a) compensation for carbohydrate metabolism within 3 months,
 - b) compensation of carbohydrate metabolism within 3 weeks,
 - c) insulin-producing function of the pancreas,
 - d) the degree of insulin resistance,
 -) the level of endogenous insulin.
5. What test is needed to determine a patient's insulin resistance?
 - a) HbA1c
 - b) blood glucose – fasting and postprandial
 - c) C-peptide
 - d) HOMA-IR
 -) OGTT
6. What parameter does not indicate absolute insulin deficiency?
 - a) high level of blood glucose
 - b) reduction of C-peptide in the blood
 - c) decrease of insulin in the blood
 - d) acetonuria

- e) diagnosi of DM in a state of ketoacidotic coma
7. What functional test allows you to diagnose insulinoma?
- a) test with cerucal
 - b) low-dose dexamethasone suppression test
 - c) high-dose dexamethasone suppression test
 - d) ACTH test
 - e) starvation test
8. What of the following DM chronic complications can lead to marked reduction in insulin need?
- a) neuropathy
 - b) nephropathy
 - c) retinopathy
 - d) microangiopathy
 - e) macroangiopathy
9. What combination of insulin preparations is not used in the scheme of basic bolus therapy?
- a) short-acting + prolonged
 - b) short-acting + long-acting
 - c) ultra-short-acting + long-acting
 - d) ultra-short-acting + prolonged
 - e) long-acting + prolonged
10. What random blood glucose level is diagnostic for DM?
- a) ≥ 7.8 mmol / L
 - b) ≥ 11.1 mmol / l
 - c) ≥ 5.5 mmol / l
 - d) ≥ 6.0 mmol / l
 - e) ≥ 7.2 mmol / l

ANSWERS: 1-b, 2-e, 3-c, 4-a, 5-d, 6-a, 7-e, 8-b, 9-e, 10-b

SELF-ASSESSMENT. SITUATIONAL TASKS

1. A 23-year-old pregnant woman with type 2 DM present to your office. She is on metformin 1000 mg 2 times daily and gliclazide MR (sulfonylurea) 60 mg before breakfast. What will be your further glucose lowering treatment tactics in this patient?
 - a) keep current therapy;
 - b) discontinue metformin, increase the dose of gliclazide MR up to 120 mg;
 - c) prescribe insulin;
 - d) diet and physical activity only;
 - e) cancel current GLT and prescribe a GLP-1 agonist.
2. A 58-year-old patient with newly diagnosed DM who recently underwent pancreatectomy for pancreatic necrosis was hospitalized. BG at hospitalization 9-12 mmol / l, acetone in the urine is absent. You will prescribe:
 - a) diet, exercises;
 - b) insulin;
 - c) metformin;
 - d) sulfonylureas;
 - e) SGLT-2 inhibitor
3. A 43-year-old patient is receiving high doses of prednisolone for bullous dermatitis. Current checkup revealed BG of 12 mmol / l, glucosuria, no acetonuria, HbA1c 7,8%. What is the most likely mechanism of DM development in this case?
 - a) autoimmune;
 - b) absolute insulin insufficiency due to atrophy of the pancreas;
 - c) relative insulin insufficiency as a result of IR caused by endogenous excess of counterinsular hormones;
 - d) relative insulin insufficiency as a result of IR caused by exogenous excess of counterinsular hormones.
4. An OGT test was carried out in a 26-year-old patient, the following glycemic parameters were detected: 4.1 mmol / l (0 min) - 9.3 mmol / l (30 min) - 8.7 mmol / l (60 min) - 7.9 mmol / l (90 min) - 7.8 mmol / l (120 min). Evaluate the test results:
 - a) norm;
 - b) impaired fasting blood glucose;
 - c) impaired glucose tolerance;
 - d) diabetes mellitus;
 - e) diabetes insipidus.
5. You were called to unconscious young woman. According to her husband, she has DM type 1 for 7 years and is on insulin therapy. Before fainting, the woman complained on headaches, feelings of heat and hunger. What will you do?
 - a) IV 40% glucose solution;
 - b) short-acting insulin 4 U SC;
 - c) prolonged-release insulin 4 U SC;
 - d) per os sweet tea;

e) IV 5 ml 2.5% solution of magnesium sulfate.

ANSWERS: 1-c, 2-b, 3-d, 4-c, 5-a

LIST OF RECOMMENDED LITERATURE

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Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

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**ВЕДЕННЯ ПАЦІЄНТІВ З ГІПЕРГЛІКЕМІЄЮ
(ЦУКРОВИМ ДІАБЕТОМ).
ВЕДЕННЯ ПАЦІЄНТІВ З ГІПОГЛІКЕМІЧНИМИ СТАНАМИ**

Методичні рекомендації
для підготовки до практичних занять здобувачів вищої медичної
освіти 6 року навчання з дисципліни «Внутрішня медицина»
(Англ. мовою)

В авторській редакції

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