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

# DIABETES MELLITUS IN CHILDREN

Methodical recommendations
for students of 5th course of medical faculty

Kharkiv – 2019

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D 44

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The methodical recommendation include traditional parts: introduction, etiology, epidemiology, pathophysiology, classification and clinical manifestations of diabetes mellitus in children at different age. Diagnostic, differential diagnosis, principles of treatment of diabetes mellitus in children were presented. This methodical recommendation include the description of the main acute complications of diabetes mellitus. Experience of determination the condition of a patient with acute complications of diabetes mellitus (comas), determination the basic principles of emergency care at coma, the ability to design a plan for further treatment is an important part of training the future physician.

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# LIST OF ABBREVIATIONS

**ADA** – American Diabetes Association
**CBC** – Complete blood count
**DM** – Diabetes Mellitus
**DKA** – Diabetic ketoacidosis
**DCCT** – Diabetes Control and Complications Trial
**FPG** – Fasting plasma glucose
**HNC** – Nonketotic hyperosmolar coma
**HbA1c** – Glycated haemoglobin
**OGTT** – Oral glucose tolerance testing
**WHO** – World health organization
**2hrPPG** – Two-hour postprandial glucose

## INTRODUCTION

***Diabetes Mellitus*** – a heterogeneous group of the metabolic diseases which are characterized by a hyperglycemia, consequence of defects of secretion of insulin, insulin action or both these factors [1, 7].

It can develop initially as an independent basic disease, or secondary as a result of another pathology.

Diabetes comes from Greek, and it means a "siphon". The word became "diabetes" from the English adoption of the Medieval Latin diabetes. In 1675, Thomas Willis added mellitus to the term and *"Mel"* in Latin means "honey"; the urine and blood of people with diabetes has excess glucose, and glucose is sweet like honey. Diabetes mellitus could literally mean "siphoning off sweet water" [13].

## EPIDEMIOLOGY

The Diabetes is one of the leading medico-social problems in the world. In Ukraine indicators of incidence of diabetes among children, in comparison with other countries of the world, it is estimated as averages - 7-19 in 100 thousand per year. Type 1 diabetes mellitus has wide geographic variation in incidence and prevalence [16]. The environmental factors are influence in the development of type 1 diabetes mellitus. Most countries report that incidence rates have at least doubled in the last 20 years. For the last 5-7 years, the prevalence of diabetes incidence among children's population is characterized by a distinct tendency to increase, and also registration of severe cases of the disease with development of its complications and a frequent disability of children [7].

Different environmental effects on type 1 diabetes mellitus development complicate the influence of race, but racial differences are evident. Whites have the highest reported incidence, whereas Chinese individuals have the lowest. Type 1 diabetes mellitus is 1.5 times more likely to develop in American whites than in American blacks [4].

The influence of sex varies with the common incidence rates. Females are at greater risk in regions of low-incidence. Males appear to be at a greater risk in high incidence regions, whose incidence rates often show seasonal variation [19].

Type 1 diabetes mellitus can occur at any age, but incidence rates generally increase with age until midpuberty and then decline. Onset in the first year of life can occur, so type 1 diabetes mellitus must be considered in any infant, because these children have the greatest risk for mortality if diagnosis is delayed. In areas with high prevalence rates, has been reported that shows a definite peak in early childhood (ie, ages 4-6 y) and a second,

much greater peak of incidence during early puberty (ie, ages 10-14 y). [18] Type 2 diabetes mellitus occurs most commonly in adults aged 40 years or older, and the prevalence of the disease increases with advancing age.

## ETIOLOGY

Although the precise cause of DM type 1 is unknown, most cases (95 %) are the result of environmental factors interacting with a genetically susceptible person. This interaction leads to the development of autoimmune process directed at the insulin-producing cells of the pancreatic islets of Langerhans. These cells are progressively destroyed, with insulin deficiency usually developing after the destruction of 90% of islet cells.

There is an increased frequency of certain histocompatibility antigens: human leukocyte antigen (HLA) class II molecules DR3 and DR4 are associated strongly with type 1 diabetes mellitus. Patients expressing DR3 are also at risk for developing other autoimmune endocrinopathies and more likely to develop diabetes at a later age, to have positive islet cell antibodies, and to appear to have a longer period of residual islet cell function. Patients expressing DR4 are usually younger at diagnosis and more likely to have positive insulin antibodies, yet they are unlikely to have other autoimmune endocrinopathies. The expression of both DR3 and DR4 carries the greatest risk of type 1 diabetes mellitus;

There is an increased incidence of DM type 1 among first-degree relatives: Monozygotic twins have a 60 % lifetime concordance for developing type 1 diabetes mellitus, dizygotic twins have only an 8 % risk of concordance, which is similar to the risk among other siblings. The frequency of diabetes development in children with a mother who has diabetes is 2-3 %; with a father - to 5-6 %. The risk to children rises to almost 30 % if both parents are diabetic [10, 14].

Neonatal diabetes (including diagnosis in infants younger than age 6 months) is most likely due to an inherited defect of the iKir6.2 subunit potassium channel of the islet beta cells, and genetic screening is indicated [7].

Environmental factors are important, because incidence rates vary in genetically similar populations under different living conditions. [18] No single factor has been identified, but infections and diet are considered the 2 most likely environmental candidates. Viral infections may be the most important environmental factor in the development of type 1 diabetes mellitus, [5] probably by initiating or modifying an autoimmune process (e.g. congenital rubella, enteroviral infection). Paradoxically, type 1 diabetes mellitus incidence is higher in areas where the overall burden of infectious disease is lower.

Dietary factors are also relevant. Breastfed infants have a lower risk for type 1 diabetes, and a direct relationship is observed between per capita cow's milk consumption and the incidence of diabetes. Some cow's milk proteins have antigenic similarities to an islet cell antigen. Nitrosamines, chemicals found in smoked foods and some water supplies, are known to cause type 1 diabetes mellitus in animal models; however, no definite link has been made with humans.

The known association of increasing incidence of type 1 DM with reduced exposure to ultraviolet (UV) light and lower vitamin D levels [9].

Additional factors in the development of type 1 diabetes mellitus include the following:

- Congenital absence of the pancreas or islet cells
- Pancreatectomy
- Pancreatic damage (ie, cystic fibrosis, chronic pancreatitis, thalassemia major, hemochromatosis, hemolytic-uremic syndrome)
- Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness)
- Chromosomal disorders such as Down syndrome, Turner syndrome, Klinefelter syndrome, or Prader-Willi syndrome

## CLASSIFICATION

**1. Etiological classification of disorders of glycemia (WHO, 2014 year)**

**1. Type 1**
**2. Type 2**
**3. Gestational diabetes**
**4. Other specific types of a diabetes:**

**a) genetic defects of function β-cells:**
- MODY-3 (chromosome12gene HNF1a);
- MODY-2 (chromosome 7, glucokinase gene);
- MODY-1 (chromosome 20gene HNF-4);
- Mitochondrial DNA mutation;
- Others.

**b) Genetic defects of effect of insulin**
- Resistance to insulin of type A;
- Leprechaunism;
- Robson Mendenhall syndrome;
- Lipoatrofi diabetes;
- Others.

**c) Diseases of exocrine part of a pancreas**
- Pancreatitis
- Neoplasia;
- Cystic fibrosis;
- Hemochromatosis;
- fibrocalculous pancreatopathy.

**d) Endocrinopathies:**
- Acromegaly;

- Cushing's syndrome;
- Glucagonoma;;
- Pheochromocytoma;
- Thyrotoxicosis;
- Somatostatinoma;
- Aldosteronoma;
- Others.

**e) diabetes induced by drugs and chemicals**:
- nicotinic acid;
- Glucocorticoids;
- Thyroidin hormones;
- Agonistics of α-adrenoceptors;
- α interferon;
- Tiazids
-others

**f) infections:**
- congenital rubella;
- cytomegalovirus;
- other.

**g) unusual forms of immunogenic diabetes:**
- «Stiff-man»- syndrom;
- autoantibodies to the insulin receptor;
- Others.

**h) other genetic syndromes sometimes combined with diabetes**:
-Down syndrome;
- Klinefelter syndrome;
Turner syndrome;
- Wolfram syndrome;
- Friedrich's ataxia;
- Huntington chorea
- Laurence-Moon-Bardet-Biedl syndrome;
- Miotonic dystrophy;
- Porphyria;
- Prader-Willi syndrome;
- Others.

**2. Clinical classification of DM type 1 by severity:**

1. **Mild** form: - Absence of ketoacidosis in anamnesis
- Absence of micro- and macroangiopathies
- Treatment consists of diet, physical exercises, phytotherapy (ideal glycemic control)

2. **Moderate** form:
- In anamnesis – ketoacidosis (I-II stages)
- Presence of diabetic retinopathy I st., diabetic nephropathy I-III st. or diabetic angiopathy I st.
- For achievement of ideal glycemic control is necessary to use insulin, or oral drug therapy or combination of both

3. **Severe** form:
- Non stable course of the disease (frequent ketoacidosis cases or coma in anamnesis)
- Presence of different chronic complications
- Patients need permanent insulin injections

**3. By glycemic control:**

A. Ideal
B. Optimal
C. Suboptimal
D. High risk for life

**4. Complication**

**I. Acute**

1. Ketoacidosis, ketoacidotic coma
2. Dehydration
3. Nonketotic hyperosmolar coma
4. Hypoglicemia, hypoglicemic coma
5. Lactoacidotic coma

**II. Chronic**

1. Angiopathy (retinopathy, nephropathy, angiopathy of legs);
2. Neuropathy (peripheral, central, autonomous);
3. Mauriac's syndrome, Nobekur's syndrome;
4. Damage of skin (dermopathy, lipoid necrobiosis, lipodystrophy, chronic paronychias);
5. Syndrome of a diabetic hand (Cheiropathie, Dupuytren's contracture);
6. Syndrome of diabetic foot, Sharko's joint.

## PATHOPHYSIOLOGY

The pancreas is located behind the stomach in the region of the 1st and 2nd lumbar vertebrae. The cells in the pancreas which produce hormones are called islets of Langerhans. The islets of Langerhans produce insulin and glucagon. Both of these hormones play a crucial role for normal regulation of glucose, lipid and protein metabolism.

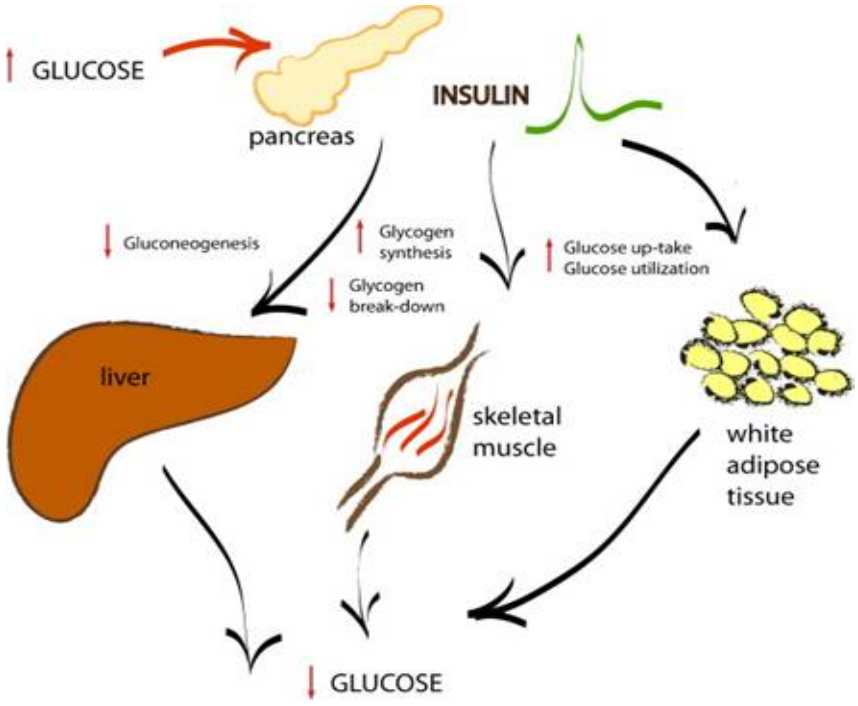


*Fig. 1. Target organs for insulin action*

Insulin is secreted in primarily in response to elevated blood concentrations of glucose. This makes sense because insulin is "in charge" of facilitating glucose entry into cells. Insulin is an anabolic hormone (promotes the synthesis of carbohydrates, proteins, lipids and nucleic acids).

The most important target organs for insulin action are:

- liver

- muscles
- adipocytes.

The brain and blood cells are unresponsive to insulin. The brain depends on glucose as a fuel. Glucose is also the sole energy source for erythrocytes and the kidney medulla.

Insulin is essential to process carbohydrates, fat, and protein. Insulin reduces blood glucose levels by allowing glucose to enter muscle cells and by stimulating the conversion of glucose to glycogen (glycogenesis) as a carbohydrate store. Insulin also inhibits the release of stored glucose from liver glycogen (glycogenolysis) and slows the breakdown of fat to triglycerides, free fatty acids, and ketones. It also stimulates fat storage. Additionally, insulin inhibits the breakdown of protein and fat for glucose production (gluconeogenesis) in the liver and kidneys. Insulin inhibits glucagon secretion, amylin inhibits insulin secretion, and somatostatin inhibits the secretion of both insulin and glucagon. All the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in the adipose tissue [6, 7, 18].

The action of insulin can be decreased by:

- glucagon: stimulates glycogenolysis and glyconeogenesis;
- somatostatin: inhibits secretion of insulin and regulates glucose absorption from alimentary tract into blood;
- glucocorticoids: decrease of glucose utilization by tissues, stimulate glycogenolysis and glyconeogenesis, increase lipogenesis (in patients with insulinoresistancy);
- katecholamines (adrenaline): inhibits β-cells secretion, stimulates glycogenolysis and ACTH secretion;
- somatotropin: stimulates α-cells (which secret glucagon), increases activity of enzymes which destroy the insulin, stimulates glyconeogenesis, increases of glucose exit from the liver veins into blood, decreases of glucose utilization by tissues;
- ACTH: stimulates glucocorticoides secretion and β-cells secretion;
- thyroid hormones: increase glucose absorption into blood, stimulate glycogenolysis, inhibit fat formation from the carbohydrates.

When 90 % of the functioning beta cells have been destroyed, loss of insulin secretion becomes clinically significant. Loss of insulin, a catabolic state develops which is characterized by decreased glucose utilization and increased glucose production (by gluconeogenesis and glycogenolysis) → hyperglycemia. Catabolic hormones (glucagon, epinephrine, growth hormone and cortisol) are elevated. These hormones stimulate lipolysis, fatty acid release and keto acid prodaction. When blood glucose is more than the renal threshold for glucose reabsorption (180mg/dl(8,8 mmol/l)), the resul-

tant glucosuria causes an osmotic diuresis with increased urine output and increased fluid intake. Ketones are produced in abundand amounts. If insulin treatment is not initiated, diabetic ketoacidosis occurs [8, 14].

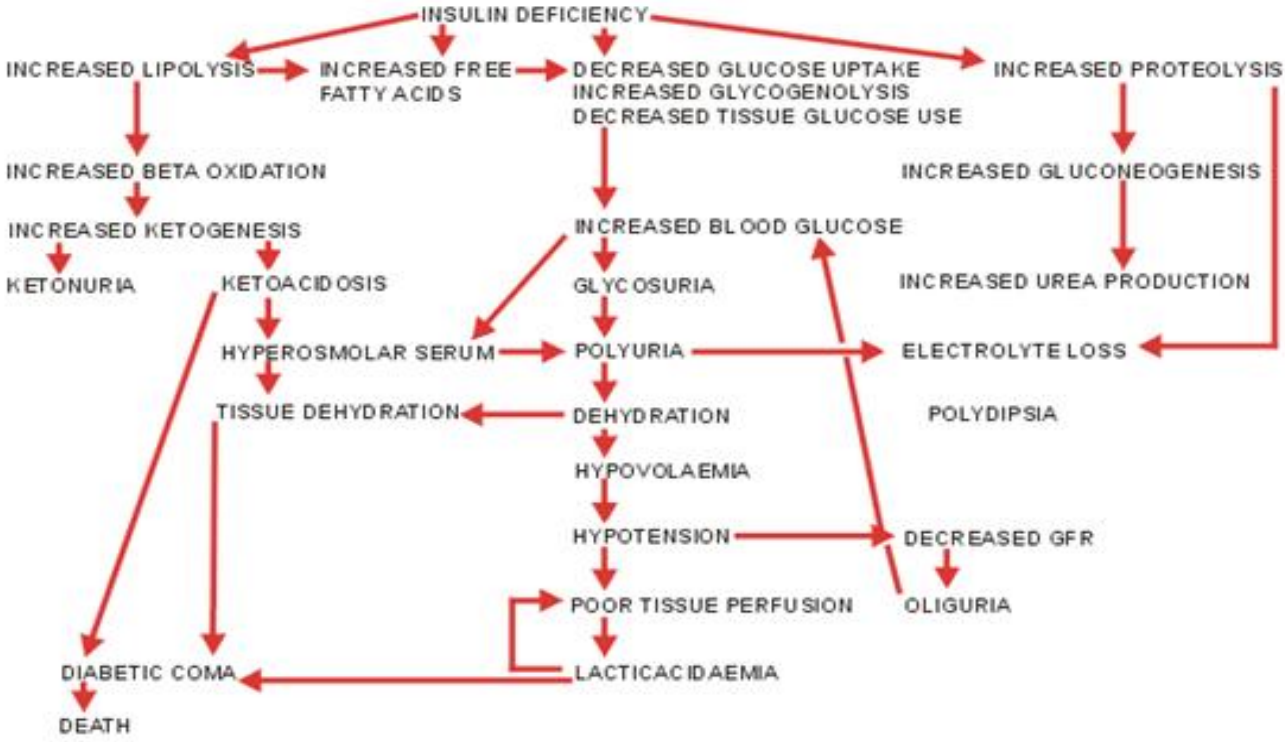


*Fig. 2. Pathogenesis of DM type 1*

**Pathogenesis of DM Type 1**

1. Influence of trigger factors on children with genetic predisposition.
2. Selective damage of beta cells.
3. Active autoimmune insulite
4. Decrease in secretion of insulin
5. Manifest diabetes mellitus
6. Full destruction of beta cells

## CLINICAL MANIFISTATIONS

1. **Clinical:**

- Polyuria;
- Polydipsia;
- Poliphagiya;
- Loss of body weight
- Bed wetting
- Dryness of mucous membranes of a mouth;
- Itch of skin and mucous;
- The increased nervous irritability;

- Headache;
- Abdominal pain, nausea, vomiting (especially decompensated ketoacidosis);
- Diabetic flush;
- An acetone smell from a mouth;
- Stomatitis, including angular stomatitis;
- Frequent infections;
- Furunculosis, hordeolum;
- Vision disorder.

**Polyuria** – secretion of urine is 2 times more than normative data. This condition leads to increased urinary frequency, which is particularly troublesome at night (eg, nocturia) and often leads to enuresis in a previously continent child. These symptoms are easy to overlook in infants because of their naturally high fluid intake and diaper/napkin use.

**Polydipsia.** Increased thirst, which may be insatiable, is secondary to the osmotic diuresis causing dehydration.

**Polyphagia** – this occurs to lack of energy.

**Weight loss.** Insulin deficiency leads to uninhibited gluconeogenesis, causing breakdown of protein and fat. Weight loss may be dramatic, although the child's appetite usually remains good. Failure to thrive and wasting may be the first symptoms noted in an infant or toddler and may precede frank hyperglycemia.

Hyperglycemia alone may not cause obvious symptoms, although some children report general malaise, headache, and weakness. Children may also appear irritable and become ill-tempered.

Hyperglycemia impairs immunity and makes a child more susceptible to recurrent infection, particularly of the urinary tract, skin, and respiratory tract. Candidosis may develop, especially in the inguinal region and in flexural areas.

**Particularities DM in infants**

- Lability of the water and mineral metabolism
- Stopping or loss body weight
- Appetite increase or normal
- Thirst, active sucking
- Starch napkins or sticky stains due to glucosuria
- Dry skin, ↓ turgor, skin infection
- Frequent illnesses and rapid growth spurts at this age can add to the difficulties with blood sugar control.

**Particularities DM in teenegers**

- Glycemic control deteriorates during puberty, which increases insulin requirement.

- There is also an increase in insulin resistance over the period of puberty.
- There is tendensy to decompensate very rapidly and develop ketoacidosis.
- Delayed of the physical and sexual development

## DIAGNOSIS

Criteria for the Diagnosis of Diabetes Mellitus: positive findings from any two of the following tests on different days:

- symptoms of diabetes mellitus + casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L)

- or FPG ≥ 126 mg /dL (7.1 mmol /L) twice

- or 2hrPPG ≥ 200 mg /dL (11.1 mmol /L) after a 1.75 g/kg glucose load

Diabetes may be diagnosed on the basis of one abnormal plasma glucose (random ≥11.1 mmol/L or fasting ≥7.1 mmol/L).

The WHO now recommends that glycated haemoglobin (HbA1c) can be used as a diagnostic test for diabetes. OGTT is not recommended as a screening test for diabetes mellitus, but if the diagnosis is still in doubt (after obligatory laboratory investigation), then perform an OGTT. [1, 7]

**Examination the patients with Diabetes Mellitus:**

**a. obligatory laboratory**

1. Fasting Plasma Glucose - one of the more common tests for diabetes, the fasting plasma glucose test, measures blood glucose for at least 8 h.

Normal blood glucose levels after a fast should be in the range of 70–100 mg/dl (3.3–5.5 mmol/l).

Mmol|L = mg| dl / 18

Typical changes: hyperglycemia;

2. Glucosuria (usually appears at the level of a glycemia of more than 180mg/dl (8,88 mmol/l));

3. Ketones in the urine - ketonuria.

4. Glycosylated hemoglobin (HbA1a, HbA1b, HbA1c) are the result of a nonenzymatic reaction between glucose and hemoglobin. A strong correlation exists between average blood-glucose concentrations over an 8-week to 10-week period and the proportion of glycated hemoglobin.

The percentage of HbA1c is more commonly measured. It works by measuring the percentage of blood sugar linked to hemoglobin, the oxygen-carrying protein in red blood cells. The higher the blood sugar level is, the more hemoglobin is that is linked with sugar. A hemoglobin A1C level of 6.5 percent or higher on two separate tests indicates diabetes. Pre-diabetes

(increased risk of developing diabetes in the future): A1c is 6.0 % - 6.5 % (39-46 mmol/ml) [1, 7].

Measurement of HbA1c levels is the best method for medium-term to long-term diabetic control monitoring. Check HbA1c levels every 3 months.

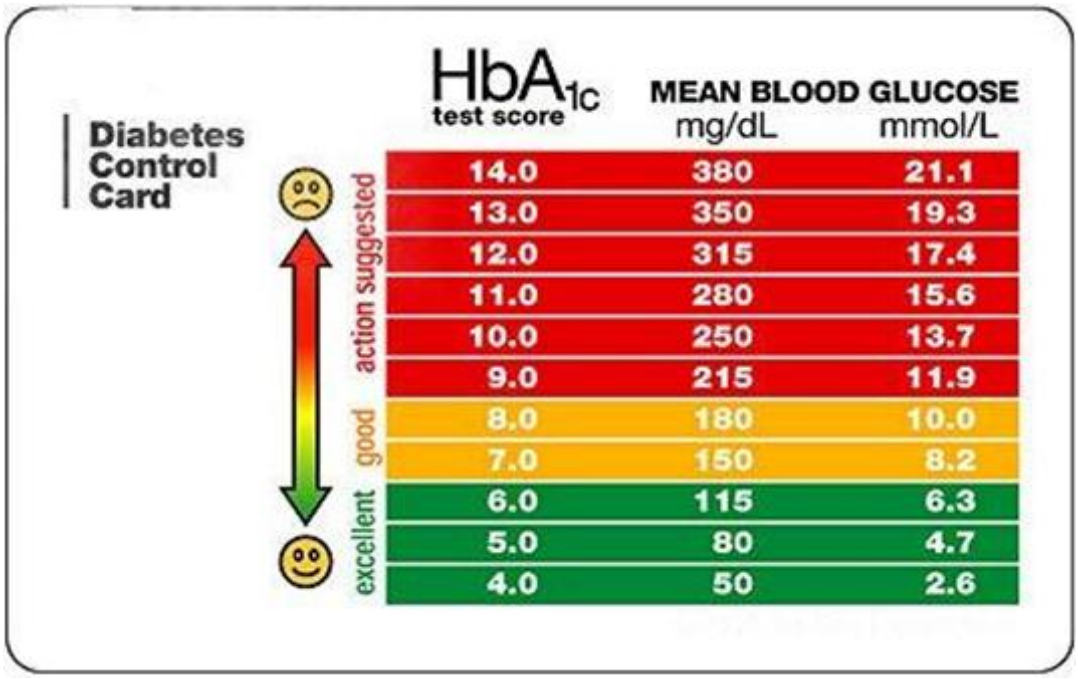


*Fig. 3. Conversion table HbA1c*

**b. Additional laboratory**

- C-peptide in serum decreased or absent;
- Increased levels of glycated hemoglobin;
- Increased levels of fructosamine;
- The presence of antibodies to antigens beta cells, insulin and different isoforms glutamic acid decarboxylase;
- Oral glucose tolerance testing (OGTT).

OGTT is a medical test in which a standard dose of glucose is administered orally & then blood sample is taken at set times to see how quickly the glucose is utilized by the body & cleared off from blood.

In the test, a person fasts overnight (at least 8 hours). Then first, the fasting plasma glucose is tested (if the first morning glycemia is higher than 8 mmol/L, oGTT is stopped). After this test, the person receives a drink containing 1.75 g/kg of glucose in 250–350 mL of water (during the period 5–15 minutes). Blood samples are taken up to four times (after 30, 60, 90 minutes and 2 hours) to measure the blood glucose level.

Diabetes mellitus is diagnosed if value of glycemia is higher than 11.1 mmol/L (≥ 200 mg/dL) after 2 hours.

Impaired glucose tolerance (IGT) :

• Fasting plasma venous glucose <7 mmol/L (<126 mg/dL); AND

• two-hour OGTT plasma venous glucose ≥7.8 mmol/L and <11.1 mmol/ L (140 to <200mg/dL).

Impaired fasting glucose (IFG) :

• Fasting plasma venous glucose measurement 6.1-6.9 mmol/L (110 to <126 mg/dL);

• two-hour OGTT plasma venous glucose <7.8 mmol/L (<140 mg/dL).

Normal: Fasting plasma venous glucose <110 mg/dL (6.1 mmol/L) 2hrPPG <140 mg/dL (7.75 mmol/L) [7, 18].

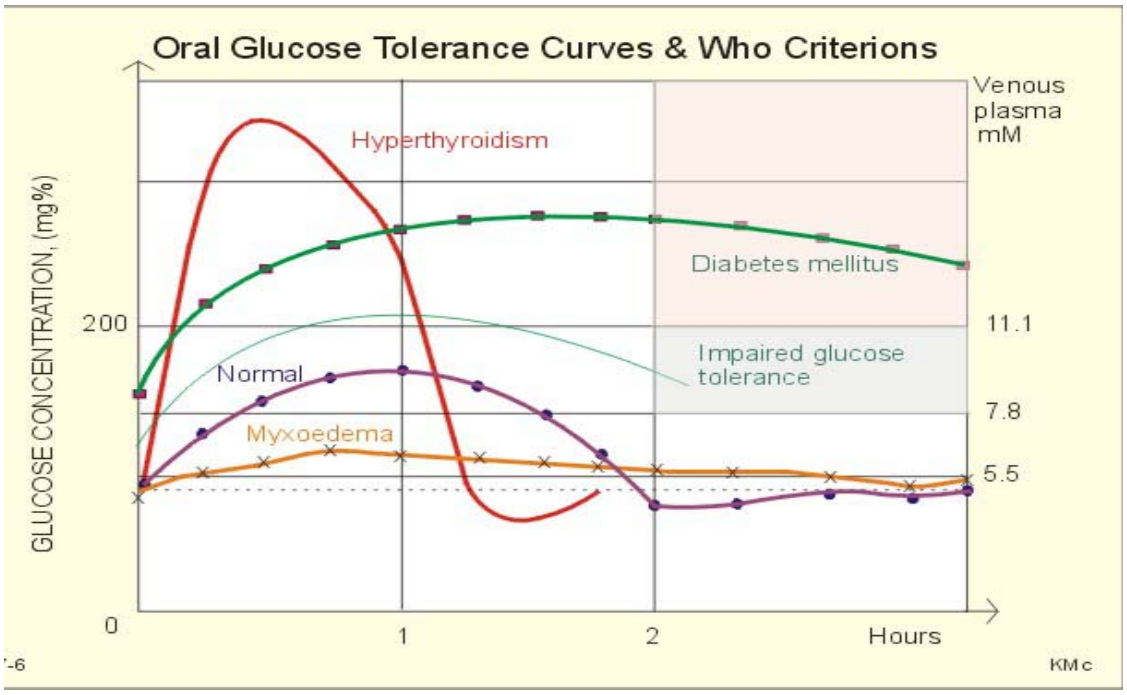


*Fig. 4. Results of Oral glucose tolerance testing*

**CRITERIES OF COMPENSATION IN CHILDHOOD**
**«Target indicators of glycemic control»**
(ISPAD Consensus guidelines, 2014)

| **The level of glycemic control** | | | | |
|---|---|---|---|---|
| | **Ideal** | **Optimal** | **suboptimal** | **High risk (requires active intervention)** |
| **Clinical assessment** | | | | |
| Raised BG | not raised | No symptoms | Polyuria, polydipsia, and enuresis | Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications |
| Low BG | Not low | No severe hypoglyce-mia | Episodes of severe Hypoglycemia (unconsciousand/or convulsions) | |

| Biochemical assessment | | | | |
|---|---|---|---|---|
| SMBG PG mmol/ L (mg/dL) AM fasting or preprandial | 3.6–5.6 (65–100) | 4–8 (70–145) | >8 (>145) | >9 (>162) |
| Postprandial | 4.5–7.0 (80–126) | 5–10 (90–180) | 10–14 (180–250) | >14 (>250) |
| Bedtime | 4.0–5.6 (80–100) | 6.7–10 (120–180) | <4.2 or >9 (<75 or >162) | <4.4 or >11 (<80 or >200) |
| Nocturnal | 3.6–5.6 (65–100) | 4.5–9 (80–162) | <4.2 or >9 (<75 or >162) | <4.0 or >11 (<70 or >200) |
| HbA1c, % (DCCT stan-dardized) | < 6.5 | <7.5 | 7.5–9.0 | > 9.0 |

- Glucose absent in urine
- Normal lipid, protein and mineral metabolism
- HbAic – 6.5-7.5 %
- The adequate growth and development of child
- Active social position in life and society
- Decreasing acute complication and prolong late complications of DM
- Normal life duration

## DIFFERENTIAL DIAGNOSIS

| By polyuria and polydipsia syndroms | By hyperglycemic syndrome | By glycosuria syndrome |
|---|---|---|
| diabetes insipidus<br>Kidney disease with chronic renal failure<br>Chronic pyelonephritis<br>primary hyperaldosteronism<br>hyperparathyreosis<br>renal diabetes<br>Neurogenic polydipsia, polyuria | Cushing's basophilism<br>Cushing's syndrome<br>steroid diabetes<br>Acromegaly<br>hemochromatosis<br>Diffuse toxic goiter<br>pheochromocytoma<br>alimentary hyperglycemia<br>neurogenic hyperglycemia<br>Diseases of a liver and pancreas | alimentary glucosuria<br>renal diabetes<br>glucosuria of pregnant women<br>kidneys diseases<br>intoxications<br>Pseudo-glucosuria |

Diabetes insipidus (DI) is defined as the passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg). DI - decreased secretion of

antidiuretic hormone (ADH). DI is characterized by a decrease in the ability to concentrate urine due to a resistance to ADH action in the kidney.

Symptoms:

- Excessive urination and extreme thirst
- low density of urine (density is a value, that indicated the concentration of substances dissolved in urine
- fever, vomiting, or diarrhea
- **No** glycosuria, hyperglycemia

Pheochromocytoma. The tumors arise from the chromaffin cells of the adrenal medulla and are associated with increased catecholamine production. Although chromaffin tissue is also present elsewhere in the body, such as in the mediastinum, along the aorta, and in the pelvis, the term pheochromocytoma is reserved for tumors that arise from the adrenal medulla. The discovery of a pheochromocytoma may indicate the presence of a familial disorder.

Symptoms: Headache, Hypertension – hyptension, hyperglycemia,

**No** Glycosuria, polyuria, polydipsia, polyphagia

Renal glucosuria. Fanconi-de Toni-Debre syndrome, cystinosis, Wilson disease, hereditary tyrosinemia, or oculocerebrorenal osteodystrophy (Lowe syndrome). Renal glycosuria has also been reported in patients with acute pyelonephritis in the presence of a normal blood glucose level. Glucose loss in the urine may vary from a few grams to more than 100 g (556 mmol) per day. Whereasmild renal glucosuria is relatively frequent, "heavy glucosuria" is extremely rare.

**No** hyperglycemia**,** polyuria, polydipsia, polyphagia.

## TREATMENT

### The main principles of treatment DM

1. Diet-therapy - eat a healthy, balanced diet, paying special attention to the amount of carbohydrates in each meal and the diabetes meal plan
2. Get regular physical activity
3. Insulin-therapy
4. Monitor blood sugar levels several times a day
5. Learning of the patient and his parents to the principles of self-control
6. Prevention and treatment of acute and chronic complications of diabetes

### 1. Diet-therapy

Dietary management is an essential component of diabetes care. Diabetes is an energy metabolism disorder, and consequently, before insulin

was discovered, children with diabetes were kept alive by a diet severely restricted in carbohydrate and energy intake. These measures led to a long tradition of strict carbohydrate control and unbalanced diets. Current dietary management of diabetes emphasizes a healthy, balanced diet that is high in carbohydrates and fiber and low in fat.

Appropritiate frequency of meals during the day: 3 main and 3 light meals; Breakfast/ lunch / supper ratio should comprise 20 % / 30 % / 20 % of a total daily intake while two snacks and a bedtime meal should consist of 10 % of the daily intake each. Also, it is important to ingest about the same amount of carbohydrates at the regullar time every day and to eat meals regullarily in order to avoid the occurrence of hypoglycemic episodes.

Daily caloric content of food for the child is calculated acording to a formula:

1000 kcal + n*100 (n – age in year) (for 0-12 year old)

1500-2000 kcal + 100 Kcal/year of age > 12 (for females 12-15)

2000-2500 Kcal+ 200 Kcal/year of age > 12 (for males 12-15)

From this amount: carbohydrates 50-55 %, fats – 30-35 %, proteins - 15-20 %.

- After calculating the number of calories attributable to carbohydrates, determine the amount *of* grain units (GU) or bread units (BU) to enable interchange of products (10-12 g carbohydrate of food are accepted for 1 BU allowing you to replace products at an equivalent amount of carbohydrates);

1 GU contains 10-12 grams of digestible carbohydrates = 50 kcal

It increases the level of blood sugar in the same magnitude – 2.8 mol/l and requires the absorption of 2 units of insulin.

The approximate daily amount of GU:

- 4-6 years old - 12-13 GU
- 7-8 years old - 15-16 GU
- 11-14 years old: boys- 18-20 GU, girls - 16-17 GU
-15–14 years old: boys– 19-21 GU, girls – 17–18 GU

The aim of dietary management is to balance the child's food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges, avoiding extremes of hyperglycemia and hypoglycemia.

Proteins are an essential nutrient, necessary for normal growth and development in childhood. Adequate protein ingestion is critical in normal muscle development. Proteins are an essential source of nitrogen. The recommended intake is 15 % of total caloric daily intake in older children and 20 % in younger. The daily requirements are about 1.5 g/kg for

preschool children for and somewhat less -1 g/kg for the children in school age. Encouraged low salt, low saturated fats and high fiber diet.

We need integrate an insulin regimen into his or her usual eating habits and physical activity schedule. Flexible insulin regimens involve multiple injections (three or more insulin injections per day) or use of an insulin infusion pump. Half of the required insulin dose is given as a basal or background insulin, and the other half is divided and given before meals (bolus or premeal insulin). These types of insulin regimens allow increased flexibility in choosing when and what to eat. The total carbohydrate content of meals is the major determinant of the mealtime rapid-acting insulin dose and postprandial glucose response. Thus, individuals can be taught how to adjust mealtime insulin doses based on the carbohydrate content of the meal and how to delay mealtime insulin for late meals [7, 17].

## 2. Physical activity

Exercise should be an integral part of the treatment plan for persons with diabetes. Exercise helps all persons with diabetes improve insulin sensitivity, reduce cardiovascular risk factors, control weight, and bring about a healthier mental outlook. Given appropriate guidelines, people with diabetes can exercise safely. The exercise plan will vary depending on interest, age, general health, and level of physical fitness [12].

The dosed exercise: morning exercise, dosed walking, therapeutic exercise, sport.

Exercise demands correction of a diet and reduction of a dose of short-acting insulin in accordance energy requirement

It is recommended to carry out exercises in 1-2 hours after meal.

Before, during and after exercises it is necessary to measure concentration of glucose in blood.

It is contraindicated intensive exercises at a glycemia is above than 12-14 mmol/l, it can provoke development of ketoacidosis.

Frequent blood glucose monitoring before, during, and after exercise helps individuals identify their response to physical activities.

## 3. Insulin-therapy

Insulin treatment must be started as soon as possible after diagnosis to prevent metabolic decompensation. Insulin has 4 basic formulations:

- ultra– short-acting (eg, lispro (Humalog), aspart (NovoLog), glulisine), starts working in 5 to 15 minutes and peaks 30 to 90 minutes later.
- traditional short-acting (eg, Actropid, Humulin R, Novolin R, regular, soluble), starts working 30 to 60 minutes after injection and generally peaks in 2 to 4 hours.

• medium- or intermediate-acting (eg, isophane, lente, detemir), starts working 1 to 3 hours after it's taken and peaks in 8 hours. NPH insulin is similar in effectiveness to long-acting types of insulin, but may be more likely to cause low blood sugar. Using NPH insulin allows for less flexibility with mealtimes, as well as in the amount of carbohydrates your child can eat.

• long-acting (eg, ultralente, glargine), has almost no peak and may provide coverage for as long as 20 to 26 hours.

Immediately after the diagnosis of diabetes is appointed a short-acting insulin subcutaneously before meals (4-6 times a day), sometimes it is possible combination of fast-acting and long-lasting insulin twice a day. In a few days it is passed to the combined administration of insulin (analogues) of the prolonged acting (before breakfast and for the night) and short-acting (before the main meals). Children and adolescents should be encouraged to inject consistently within the same site (abdomen, thigh, buttocks, and arm) at a particular time in the day, but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy.

***Daily doses of insulin:***

- The debut of diabetes - 0.5-0.6 U / kg;
- The period of remission - <0.5 U / kg;
- Long-term diabetes - 0.7-0.8 U / kg;
- Decompensation (ketoacidosis) - 1.0-1.5 U / kg;
- prepubertal period; - 0,7-1,0 U/ kg;
- The puberty - 1,2-2,0 U/ kg;.

The choice of insulin regimen will depend on many factors including: age, duration of diabetes, lifestyle (dietary patterns, exercise schedules, school, work commitments, etc.) Insulin regimen

• Basis permanent Insulin secretion (imitation by long acting Ins)

• Bolus (imitation of stimulation Insulin secretion) – short Insulin

With so many various insulins and mixtures available, a wide range of possible injection regimens exist. These can be broadly categorized into 4 types, as follows:

• Twice-daily combinations of short- and intermediate-acting insulin.

• Multiple injection regimens using once-daily or twice-daily injections of long-acting insulin and short-acting insulins given at each meal (The Basal-Bolus Insulin Concept)

• A combination of the above 2 regimens, with a morning injection of mixed insulin, an afternoon premeal injection of short-acting insulin and an evening injection of intermediate- or long-acting insulin

• Continuous subcutaneous insulin infusion (CSII) using an insulin pump

Although controlled clinical trials suggest improved short-term metabolic control in children using multiple injections international compari-

sons do not support any particular insulin regimen, and all have their advantages and disadvantages [3, 7].

4. Monitoring at patient with DM:

- HbA1c every 3-months
- Home regular blood glucose monitoring
- Home urine ketones tests

Education is the key to successful management of diabetes. There is evidence that educational interventions in childhood and adolescent diabetes have a beneficial effect on glycemic control and on psychosocial outcomes.Diabetes education needs to be adaptable and appropriate to each individual's age and maturity. Educate child and care givers about: diabetes, insulin, life-saving skills, recognition of hypoglycemia and DKA, meal plan, regular glycemic control.

## ACUTE COMPLICATIONS OF DM

### Hypoglycemia, hypoglycemic coma

Symptoms of hypoglycemia:

- Dizziness, headache,
- Nervousness, feeling of anxiety,
- disorders of coordination of movements,
- Pale skin,
- Numbness in the fingertips,
- tremulousness
- Sweating, palpitation
- Disturbances of consciousness, possible fainting, seizures, coma and even death result.

Laboratory findings: low level of blood glucose.

Treatment of Hypoglycemia:

- Consciousness is present (1-2 tea spoons of sugar or honey or 5-6 pieces of hard candy, 1 cup of juice or milk; in 15 min – sandwich, crackers)
- Consciousness is absent Glucagon s/c or i/m < 5 yrs old - 0.5 mg, >5 yrs old - 1 mg,
- 20% Glucose 1 mL/kg -3 min, than 10% Glucose 2-4 mL/kg

### Diabetic ketoacidosis (DKA). Ketoacidotic coma

**Diagnostic criteria:** 1) Hyperketonemia (> 3mmol/L) and Ketonuria (> 2+ on standard urine sticks) 2) Hyperglycaemia (blood glucose > 200mg/dL) 3) Metabolic acidosis (venous bicarbonate <15mmol/L and/or venous pH<7.3)

DKA develops over a period of days or weeks.

Signs and symptoms:

1. Polydipsia, polyuria and weakness are the most common presenting complaints.

2. Anorexia, nausea, vomiting, and abdominal pain may be present and mimic an abdominal emergency.

3. Kussmaul breathing (deep, sighing respiration) is present as respiratory compensation for the metabolic acidosis and is obvious when the pH is less than 7,1.

4. Symptoms of central-nervous-system involvement include headaches, drowsiness, fatigue, stupor and coma (only 10 % patients are unconscious).

## Treatment

1. Reduction of hyperglycemia.

Initial intravenous administration of insulin (short-acting) in a dose 0,1 unit/kg/hour in 0,9 % sodium chloride infusion has to be given. If the glucose level does not improve (decrease on 3,3-5,5 mmol/l) after an hour of infusion, the rate of insulin is doubled until a response is noted. But if there is a tendency for quicker decreasing the level of glucemia we have to decrease the dose of insulin in twice. When the level glucose concentration reaches 11-13 mmol/l, insulin can be given subcutaneously.

2. Rehydratation.

1st hour – 10-20 mL/kg i/v bolus 0.9 % NaCl or Lactate Ringer2nd hour until DKA resolution – 10 mL/kg 0.45 % NaCl

Fluid deficiency = Degree dehydration (%) + maintenance daily fluid

<1 year old (3-9 kg) – 80 mL/kg/hr
1-5 yrs old (10-19 kg) – 70 mL/kg/hr
6-9 yrs old (20-29 kg) – 60 mL/kg/hr
10-14 yrs old (30-50 kg) – 50 mL/kg/hr
>15 yrs old (>50 kg) – 35 mL/kg/hr

When serum glucose level is about 11–13 mmol/l administration of 5 % glucose with insulin can be performed (1 to 2 unites of insulin on each 100 ml of 5 % glucose solution). The addition of glucose to the intravenous solution is necessary for correction of tissue lipolysis and acidosis.

3. Correction of: a) acid-base and b) electrolyte imbalance.

Potassium 5% glucose if blood suger < 14 mmol/L

PH<7.0- Na bicarbonate 1-2 mmol/kg- 1-2 hours

4. Investigation of precipitating factors, treatment of complications. [8]

## Nonketotic hyperosmolar coma

HNC is a syndrome characterized by impaired consciousness, sometimes accompanied by seizures, extreme dehydration and extreme hyperglycemia that is not accompanied by ketoacidosis.

Diagnostic criteria

Signs and symptoms

1. Polyuria, polydipsia, weight loss, weakness and progressive changes in state of consciousness from mental cloudiness to coma (present in 50 % of patients) occur over a number of days to weeks.

2. Because other underlying conditions (such as cerebrovascular accident and subdural hematoma) can coexist, other causes of coma should be kept in mind, especially in the elderly.

3. Seizures occur in 5 % of patients and may be either focal or generalized.

Physical examination

1. Severe dehydration is invariably present.

2. Various neurologic deficits (such as coma, transient hemiparesis, hyperreflexia, and generalized areflexia) are commonly present. Altered states of consciousness from lethargy to coma are observed.

3. Findings associated with coexisting medical problems (e.g., renal disease, cardiovascular disease) may be evident.

Laboratory findings

1. Extreme hyperglycemia (blood glucose levels from 30 mmoll/l and over ).

2. A markedly elevated serum osmolality, usually in excess of 350 mOsm/l. (Normal = 290 mOsm/l). The osmolality can be calculated by the following formula: mOsm/l = 2(Na + K) = blood glucose/18 + BUN/2.8.

3. The initial plasma bicarbonate averaged.

4. Serum ketones are usually not detectable, and patients are not acidic.

5. Serum sodium may be high (if severe degree of dehydration is present), normal, or high (when the marked shift of water from the intracellular to the extracellular space due to the marked hyperglycemia is present).

6. Serum potassium levels may be high (secondary to the effects of hyperosmolality as it draws potassium from the cells), normal, or low (from marked urinary losses from the osmotic diuresis). But potassium deficiency exists.

Treatment:

- rehydration;
- reduction of hyperglycemia;
- electrolytes replacement;
- investigation of precipitating factors, treatment of complications.

## Lactoacidotic coma

Signs and symptoms:

1. Kussmaul breathing

2. headaches, drowsiness, fatigue.

3. Anorexia, nausea, vomiting, and abdominal pain may be present.
4. Myalgia.
Physical examination:
1. Tachycardia, blood pressure is decreased
2. Acrocyanosis.
3. Poor skin tugor and dry skin.
4. Hypothermia
5. Tachypnea
Laboratory findings:
1. Blood glucose level is not high
2. Glucosuria is absent.
3. Blood lactic acid is high.
Treatment: - correct the underlying cause.
- in severe cases, bicarbonate therapy should be used (intravenously-infused Na bicarbonate 1-2 mmol/kg- 1-2 hours).
- can be prescribe low dose insulin regimens with 5 % glucose solution infusion.

## CONTROL TESTS

**1.** A 3-year-old child has been diagnosed with type I diabetes mellitus, hyperosmolar coma. The laboratory confirmed the diagnosis. Which laboratory findings are characteristic for such condition?
A. High hyperglycemia without ketonemia
B. Hyperglycemia and ketonemia
C. Hyperglycemia and glucosuria
D. Hyperglycemia and ketonuria
E. Hyperglycemia and high indicators of acid-base balance
**2.** An 8-year-old child with a 3-year history of diabetes was hospitalized in hyperglycemic coma. Specify the initial dose of insulin to be administered:
A. 0,3-0,4U/kg of body weight per hour
B. 0,05 U/kg of body weight per hour
C. 0,2-0,3 U/kg of body weight per hour
D. 0,1-0,2 U/kg of body weight per hour
E. 0,4-0,5 U/kg of body weight per hour
**3.** A 16-year-old girl had had polyuria, polydipsia for 2 months. She had lost 8 kg with a good appetite. The patient was urgently hospitalized for abdominal pain and nausea. Examination revealed glycemia at the rate of 18 mmol/l, glycosuria at the rate of 24 g/l. Insulin and infusion of isotonic solutions of sodium chloride and glucose eliminated these problems, including thirst. What is the most likely diagnosis?
A. Diabetes insipidus

B. Diabetes mellitus type 2
C. Renal glycosuria
D. Diabetes mellitus type 1
E. Secondary (symptomatic) diabetes

**4.** A 10-year-old girl consulted a doctor about thirst, frequent urination, weight loss. She has been observing these symptoms for about a month. Objectively: no pathology of internal organs was revealed. What laboratory analysis should be carried out in the first place?

A. Blood glucose analysis on an empty stomach
B. Glucose in urine test on the base of daily diuresis
C. Acetone in urine test
D. Glucose tolerance test
E. Glucosuric profile

**5.** A patient with diabetes mellitus suffers from persistently nonhealing surgical wound, which is a sign of disrupted tissue trophism. What is the cause of such disorder?

A. Disruption of protein metabolism regulation
B. Ketonemia
C. Anemia
D. Increased lipid catabolism
E. Hypoglycemia

**6.** A 16 –year old person complains of thirst, poliuria, general weakness, loos of body weight. The objective picture shows: the skin is dry, red cheeks, vesicular respiration. The heart tones are sound. The of heart soundings. The tongue is dry. There are no symptoms of irritation of the peritoneum. What investigation is the most informative?

A. General urine analysis
B. General blood analysis
C. Diagnosing blood on sugar
D. Urine analysis by Zimnitskiy
E. Blood analisis on liver function tests

**7.** How to estimate the test of tolerance to glucose for a 16-years-old boy on an empty stomach - 5,78 mmol/l, in 1 hour after the intake of 75 grammes of glucose - 7,21 mmol/l, in 2 hours - 5,68 mmol/l?

A. Tolerance to glucose is not disturted.
B. Diabetes mellitus of moderate form.
C. Diabetes mellitus of latent form.
D. Diabetes mellitus of mild form.
E. Symptomatic hyperglycemia

**8.** A 13-year old patient with first found diabetes mellitus with the help of a diet supports glycemia after meals less than 10,0 mmol/l. He refrains

from insulinotherapy. What investigation is the most important to conduct for the differentiation of the 1st and 2 nd types of diabetes?

A. Defining antibodies to the islet cells

B. Glucose-tolerant test.

C. Research of glycemia on an empty stomach

D. Determination of HbAc1

E. Determination of fructosamine of blood

Standard responses: 1 – A; 2 – D; 3 – D; 4 – A; 5 – A; 6 – C; 7 – A; 8 – A.

## THE CONTROL QUESTIONS

1. Leading clinical symptoms of syndrome of hyperglycemia in children.
2. Leading clinical symptoms and syndromes in diabetes in children.
3. Features of a course of diabetes in children depending on severity and level control.
4. Data of laboratory and instrumental studies at diabetes in children
5. Differential diagnosis of the syndrome of hyperglycemia in children of all ages.
6. Establishing a preliminary diagnosis of syndrome of hyperglycemia in children..
7. Clinical management of patients with the syndrome of hyperglycemia, various clinical variants course of diabetes in children.
8. Provision of emergency care at the syndrome of hyperglycemia and acidosis.
9. Prevention of diabetes and its complications in children of different ages.
10. The main reasons for learning of the patient the to the principles of self-control.

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