



DISORDERS OF CARBOHYDRATE METABOLISM IN CLINICAL PRACTICE

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Abstract. This article examines the possibilities for the timely and accurate diagnosis of carbohydrate metabolism disorders in clinical practice. Given the prevalence of diabetes mellitus (DM), the rapid development of complications, the significant number of undiagnosed cases, and concerning projections regarding the future spread of the disease, the importance of early diagnosis of carbohydrate metabolism disorders is emphasized. Definitions and current 2017 guidelines from the American Diabetes Association regarding diagnostic criteria for impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus are presented. The significance of insulin resistance and the functional status of pancreatic beta-cells in predicting the course and determining the duration of type 2 diabetes mellitus is highlighted. An examination plan for individuals with newly diagnosed type 2 diabetes mellitus is provided.

Keywords: diabetes mellitus; impaired fasting glucose; impaired glucose tolerance; insulin resistance; diagnosis.

Introduction

The current epidemic of type 2 diabetes (CD) is just the tip of the iceberg, as most endocrinologists have said. The development of type 2 CD is due to the respect of practical symptoms of disturbances in carbohydrate metabolism—impaired glycemia in nature (PGN) and impaired glucose tolerance (PTH). In connection with these remaining issues, the nutritional immediate primary prevention of type 2 CD and associated cardiovascular disease (CVD) is widely discussed. Here, according to the technical advice of the WHO, PTH and PGN are included in the understanding of prediabetes and early disturbances in carbohydrate metabolism.

Circulatory diabetes (CD) is a group of metabolic (metabolic) diseases that are characterized by chronic hyperglycemia resulting from impaired secretion of insulin, insulin, or both officials Chronic hyperglycemia in CD is accompanied by stress, dysfunction and deficiency of various organs, especially the eyes, eyes, nerves, heart and blood vessels (Ministry of Health of Uzbekistan, 2014). What is important is the greater number of drops in the Central Bank on- fall into two great etiological and pathogenic categories.

CD type 1 is characterized by an absolute deficiency of insulin secretion. The study of the pathophysiological features of CD type 1 allowed us to establish that the constant presence of two or more autoantibodies in people of the first stage of pregnancy with diseases of CD type 1 can be seen in Most seizures are indicative of clinical hyperglycemia and diabetes. The fluidity of progression remains in the eye at the time of detection of antibodies, their titer and specificity. Levels of glycemia and glycated hemoglobin (HbA1c) move just before the clinical beginning of CD, confirming the diagnosis even before the development of diabetic ketoacidosis. Today we have seen three clear stages of development of type 1 CD (Table 1).

Stage	First	Second	Third
Signs	Autoimmunity (a state of aggression against one's own cells). Normoglycemia. Presymptomatic.	Autoimmunity. Dysglycemia. Presymptomatic	Newly detected hyperglycemia. Symptoms
Diagnostic criteria	Multiple autoantibodies. PTH and PGN absent.	Multiple autoantibodies. Dysglycemia: — IFG and/or IGT; — fasting plasma glucose 5.6–6.9 mmol/L; — 2-hour plasma glucose 7.8–11.0 mmol/L; — HbA1c 5.7–6.4%, or an increase in its level by 10%	Clinical symptoms of diabetes mellitus according to standard criteria

Table 1. Stages of type 1 diabetes development (Skyler J.S. et al., 2016; Insel R.A. et al., 2015)

In type 2 CD, the mechanisms of development of beta-clitin dysfunction are less pronounced. Type 2 CD is caused by a combination of insulin resistance and inadequate insulin secretion. For which type of CD the level of hyperglycemia is sufficient to lead to pathological and functional changes in target organs; however,



this hyperglycemia does not yet cause clinical symptoms and may persist for a long period before diabetes is detected.

Macrovascular complications (primarily myocardial infarction) pose the main threat to patients with type 2 diabetes mellitus (T2DM), accounting for 65% of total mortality. Chronic hyperglycemia is considered one of the factors contributing to the elevated cardiovascular risk associated with T2DM.

It is known that more than 80% of patients with T2DM are overweight or obese. According to the NHANES study (USA, 1999–2000), the prevalence of T2DM among overweight individuals was 2.9 times higher than in the population with a normal body weight. With a body mass index (BMI) exceeding 30 kg/m², the risk of developing T2DM is 27.6 times higher than with a BMI of 22 kg/m². In 2013, cardiovascular diseases (CVD) accounted for 66.5% of the total mortality in Uzbekistan (Mitchenko O.I., 2015). Cardiovascular diseases account for 80% of deaths among patients with diabetes mellitus, which necessitates early diagnosis and appropriate treatment of diabetes and obesity.

Between 2009 and 2013, a research project was conducted to study 20 risk factors within the urban population of Dnipropetrovsk, based at five of the city's outpatient clinics. According to this population-based study, only 29.3% of the population had a normal body weight, while 70.7% fell into the categories of excess body weight or obesity (grades I–III). Specifically, 39.18% had excess body weight, 22.75% had grade I obesity, 7.78% had grade II obesity, and 1.03% had grade III obesity. The total prevalence of all carbohydrate metabolism disorders among the urban population in Ukraine was 77.2%. Within this group, insulin resistance (IR) was detected in 41.2% of respondents, pre-type 2 diabetes (PT2D) in 28%, and type 2 diabetes mellitus (T2DM) in 8% of the total population (Mitchenko O.I. et al., 2013).

As body weight increased, the prevalence of IR rose from 16.8% in individuals with a normal body weight to 77.2% in those with grade II–III obesity; the prevalence of PT2D increased from 23.4% to 36.9%, and the prevalence of T2DM rose from 3.4% to 16.3%, respectively. The development of abdominal obesity in men is accompanied by an exacerbation of carbohydrate metabolism disorders, with the prevalence of insulin resistance (IR) increasing by 35.4%, prediabetes (PD) by 5.6%, and type 2 diabetes mellitus (T2DM) by 8.3%. In women, the presence of abdominal obesity is associated with a 7.8% higher prevalence of IR and a 5.0% higher prevalence of PD compared to women without abdominal obesity (Mitchenko O.I. et al., 2013).

Numerous prospective studies have demonstrated that early carbohydrate metabolism disorders—specifically prediabetes—are independent risk factors for cardiovascular disease (CVD). The use of antihyperglycemic agents in individuals with prediabetes helps reduce the incidence of both type 2 diabetes and the overall rate of cardiovascular events. Therefore, identifying individuals with early carbohydrate metabolism disorders and implementing preventive interventions is of significant medical and social importance. If screening is properly organized within patient



groups at high risk for carbohydrate metabolism disorders, successful primary prevention of type 2 diabetes during the prediabetes stage can contribute to a substantial reduction in both macrovascular and microvascular complications.

Therefore, assessing insulin resistance using the HOMA-IR index is recommended for individuals with excess body weight or obesity (especially dysplastic obesity), arterial hypertension, gout, dyslipidemia, ischemic heart disease (IHD), other endocrine disorders (such as hypothyroidism, Cushing's syndrome, acromegaly, pheochromocytoma, hirsutism, etc.), polycystic ovary syndrome (PCOS), and infertility.

Diagnosis of early carbohydrate metabolism disorders

The blood test for glycated hemoglobin (HbA1c) offers advantages over fasting blood glucose testing and the 2-hour glucose tolerance test. These advantages include the following: the HbA1c test can be performed at any time—fasting is not required; it is more accurate than a fasting blood glucose test, allowing for the earlier detection of prediabetes and diabetes mellitus (DM); it is faster and simpler to conduct than a 2-hour glucose tolerance test; it provides a clear answer as to whether an individual has prediabetes or diabetes mellitus; it helps determine how well a person with diabetes has controlled their blood sugar levels over the past three months; and the HbA1c result is not affected by common colds or stressful situations.

The HbA1c test result is independent of the time of day the blood sample is collected or whether the individual has recently eaten. ...the use of medications (other than oral antidiabetic drugs), physical exertion, a person's emotional state, as well as colds and other infections; furthermore, it exhibits significantly lower biological variability compared to blood glucose measurements.

An HbA1c blood test allows for the detection of diabetes at an early stage—even when a fasting blood glucose test still indicates that everything is normal within the body.

Measuring HbA1c allows for the differentiation between stress-induced hyperglycemia and previously undiagnosed diabetes mellitus. HbA1c is a specific compound formed by the binding of glucose to hemoglobin within red blood cells; its concentration reflects the average blood glucose level over a period of approximately three months. Hemoglobin is a protein found inside red blood cells that transports oxygen. While there are several types of normal hemoglobin, various abnormal variants have also been identified; hemoglobin A is the predominant form, accounting for 95–98% of total hemoglobin. Hemoglobin A consists of several components, one of which is glycated. A portion of the glucose circulating in the blood binds spontaneously to hemoglobin, forming what is known as glycated hemoglobin. The higher the blood glucose concentration, the greater the amount of HbA1c produced. HbA1c accumulates within red blood cells and persists throughout their entire lifespan. HbA1c is continuously formed and removed from the bloodstream as older red blood cells die and are replaced by younger ones (which are not yet glycated). Since circulating red blood cells vary in age, it is recommended to



consider the half-life of red blood cells—approximately 60 days—when interpreting these levels. The concentration of HbA1c reflects a patient's glycemic status over the 60 (up to 90) days prior to the test. The most significant impact on HbA1c levels comes from the 30 days immediately preceding the sample collection; glycemic levels during this period account for up to 50% of the total HbA1c value. Consequently, the value of measuring HbA1c lies in its ability to characterize the state of carbohydrate metabolism over the preceding 2–3 months. When evaluating HbA1c, one must consider the specific measurement method employed and the analytical reliability of that method. Until a few decades ago, there was no standardization of HbA1c measurement methods, which limited the clinical utility of the test. In 1993, the American Association for Clinical Chemistry established the National Glycohemoglobin Standardization Program (NGSP). Currently, manufacturers of HbA1c test systems are required to undergo verification and obtain certification of traceability to the Diabetes Control and Complications Trial (DCCT). The American Diabetes Association recommends that all laboratories use only NGSP-certified tests. The use of standardized methods enables laboratories to produce the most reliable test results. Therefore, in routine clinical practice, when reviewing an HbA1c result, a physician should verify whether the test was performed in a standardized laboratory. It is extremely important that physicians use results obtained only from laboratories that perform HbA1c testing using methods certified by the NGSP.

This, in accordance with current international recommendations from leading diabetes associations, indications for HbA1c testing include: screening for and diagnosis of diabetes mellitus (DM); monitoring the course of the disease and the effectiveness of treatment in patients with DM (including the assessment of glycemic control); evaluating pregnant women to diagnose gestational diabetes and assess the risk of congenital fetal abnormalities; and estimating the risk of macrovascular and microvascular complications of DM.

In patients belonging to a high-risk group, it is impossible to determine individual glucose tolerance without performing a glucose tolerance test (GTT). According to WHO recommendations, the GTT is conducted as follows: after a blood sample is collected to measure fasting glucose levels, the patient consumes 75 g of glucose dissolved in 100 ml of water. The intake should be completed within no more than five minutes. In healthy individuals, blood glucose concentration begins to rise 15–20 minutes after glucose ingestion, reaching a peak within the first hour (between 30 and 60 minutes). Subsequently, glucose levels begin to decline; by the second hour (120 minutes), the level either returns to the baseline (fasting) value or drops slightly below it. By the third hour, blood glucose levels return to the baseline.

The initial rise in glucose levels following a glucose load reflects the intensity of the reflex stimulation of the sympathetic nerves triggered by the entry of glucose into the gastrointestinal tract. The subsequent increase in blood glucose concentration is generally associated with the rate of carbohydrate absorption and liver function. In a healthy individual, the blood glucose concentration one hour after the load is 50–

75% higher than the fasting glucose level. The descending limb of the curve reflects insulin production and depends on the functional state of the parasympathetic nervous system and the function of the pancreas; this segment of the curve is known as the hypoglycemic phase. The final point on the glycemic curve—determined at 2.5–3 hours, or at 3.5–4 hours in cases of impaired glucose tolerance—indicates the status of the glucose utilization system. Under normal conditions, this value should be equal to the fasting blood glucose level or 10–15% lower.

The diagnosis of diabetes mellitus (DM) is based on plasma glucose levels, specifically: fasting plasma glucose (FPG), plasma glucose 2 hours after a glucose tolerance test (GTT), or HbA1c.

Diagnostic criteria for diabetes mellitus (ADA, *Standards of Medical Care in Diabetes — 2017*):

- FPG > 7.0 mmol/L following an 8-hour fast, or
- plasma glucose > 11.1 mmol/L 2 hours after a GTT (using a 75 g glucose load), or
- HbA1c > 6.5% (measured via a standardized method), or
- presence of classic symptoms of hyperglycemia combined with a plasma glucose level > 11.1 mmol/L.

Criteria for diagnosing DM or prediabetes in asymptomatic individuals (ADA, *Standards of Medical Care in Diabetes — 2017*):

1. Screening of adults who are overweight or obese (BMI > 25 kg/m²) and have one or more of the following risk factors:
 - HbA1c > 5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) identified during previous examinations;
 - first-degree relatives with diabetes mellitus;
 - women with a history of gestational diabetes mellitus;
 - a history of cardiovascular disease;
 - arterial hypertension (> 140/90 mmHg or use of antihypertensive therapy); — high-density lipoprotein cholesterol (HDL-C) level < 0.90 mmol/L and/or triglycerides > 2.82 mmol/L;
 - women with polycystic ovary syndrome;
 - insufficient physical activity;
2. For all patients, screening begins at the age of 45.
3. If screening results are normal, they should be repeated at least every 3 years.

Criteria for increased risk of developing diabetes mellitus (prediabetes) (ADA, Standards of Medical Care in Diabetes — 2017):

- fasting plasma glucose from 5.6 to 6.9 mmol/L, or
- plasma glucose 2 hours after an oral glucose tolerance test (OGTT) from 7.8 to 11.0 mmol/L, or
- HbA1c 5.7–6.4%.



Gestational Diabetes Mellitus

For many years, gestational diabetes mellitus (GDM) has been defined as any degree of glucose intolerance first identified during pregnancy. The global epidemic of obesity and diabetes has led to an increased prevalence of type 2 diabetes among women of reproductive age, as well as a rise in the number of pregnant women with undiagnosed type 2 diabetes. Given the significant proportion of pregnant women with undiagnosed type 2 diabetes, it is advisable to screen women with risk factors for diabetes during their first prenatal visit, using standard diagnostic criteria. Diabetes diagnosed in the first trimester should be classified as pre-existing (pregestational) diabetes (type 2 diabetes or, very rarely, type 1 diabetes). Therefore, it is more accurate to define gestational diabetes as diabetes that is first diagnosed during the second or third trimester of pregnancy. The following are recommendations regarding the screening and diagnosis of gestational diabetes (ADA, *Standards of Medical Care in Diabetes — 2017*).

The one-step strategy involves performing an oral glucose tolerance test (OGTT) with a 75 g glucose load, measuring plasma glucose levels while fasting, as well as one and two hours post-load, between the 24th and 28th weeks of pregnancy in women who did not previously have overt diabetes. The GTT (glucose tolerance test) is performed in the morning following an overnight fast of at least 8 hours.

A diagnosis of gestational diabetes mellitus (GDM) is established if any of the following values are observed (or exceeded):

- fasting: 5.1 mmol/L;
- at 1 hour: 10.0 mmol/L;
- at 2 hours: 8.5 mmol/L.

In Ukraine, according to Ministry of Health Order No. 582 dated December 15, 2003, women in high-risk groups are subject to mandatory screening for gestational diabetes. This group includes pregnant women who present with one or more of the following risk factors:

- diabetes mellitus in parents or close relatives;
- gestational diabetes during a previous pregnancy;
- obesity;
- a history of giving birth to an infant weighing over 4,000 g;
- a history of stillbirth;
- polyhydramnios;
- glycosuria detected on two occasions.

An indication for screening for gestational diabetes mellitus (GDM) is also a fasting plasma glucose level ≥ 5.83 mmol/L or a fasting capillary blood glucose level ≥ 5.0 mmol/L. The diagnosis of GDM is carried out in two stages. The first stage involves a one-hour glucose tolerance test (GTT) with a 50 g glucose load (screening test). If the result is positive, the diagnosis is confirmed using a three-hour GTT with 100 g of glucose. The one-hour GTT can be performed at any time of day; it does not



necessarily require a fasting state. The pregnant woman is given 50 g of glucose dissolved in 200 ml of water (lemon juice may be added). One hour later, the plasma glucose level is measured from venous blood. If the glucose level is < 7.8 mmol/L, glucose tolerance is considered normal. If the glucose level is ≥ 7.8 mmol/L, a three-hour GTT is indicated; furthermore, if the level exceeds 10.55 mmol/L, a preliminary diagnosis of GDM is made.

The three-hour GTT is mandatory for establishing a definitive diagnosis. For at least three days prior to the test, the pregnant woman must follow her usual diet, without restricting carbohydrate intake. In the morning, on an empty stomach—at least 12 hours after the last meal—a "butterfly" needle or catheter is inserted into a vein, and a blood sample is collected. The patient is then given 100 g of glucose, dissolved in 250–300 ml of water with added lemon juice. Blood samples to determine glucose levels are collected at 1, 2, and 3 hours. Throughout the entire procedure, the pregnant woman must remain at rest (sitting or lying down) and must not eat or smoke. Drinking water is permitted. It is possible to measure glucose levels in whole capillary blood rather than in venous plasma; however, results obtained in this manner are considered less accurate.

Indicators	Definition
Carbohydrate metabolism	Glycemia (fasting, postprandial), HbA1c, blood insulin (C-peptide), insulin resistance index, HOMA-IR, antibodies to glutamic acid decarboxylase (in the absence of obesity)
Lipid metabolism	Total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, atherogenic index, leptin
Anthropometric indicators	Body mass index, waist circumference, hip circumference
Cardiovascular system	Blood pressure, heart rate, electrocardiography (cycle ergometry), echocardiography, Doppler ultrasound of cerebral and lower limb vessels
Kidneys	Ultrasound, urinalysis, albuminuria (microalbuminuria), creatinine, urea, glomerular filtration rate
Endocrine system	Thyroid ultrasound, thyroid-stimulating hormone, free testosterone (for men), pelvic ultrasound (for women)
Purine metabolism	Uric acid
Vitamins and Mineral Metabolism	Vitamin D, vitamin B12 (considering ongoing metformin use), ionized calcium, potassium, sodium, magnesium, phosphorus, chlorides
Liver	Ultrasound, bilirubin, albumin, activity of alanine transpeptidase, aspartate transaminase, γ -glutamyl transpeptidase, and alkaline phosphatase, thymol turbidity test results
Eyes	Ophthalmologist consultation
Nervous system	Neurologist consultation



Psychological state	Psychotherapist consultation
Living with Diabetes	Diabetes Self-Management Education Schools

Table 2. Recommended assessment plan for individuals with newly diagnosed type 2 diabetes mellitus

Notes: LDL-C — low-density lipoprotein cholesterol; VLDL-C — very-low-density lipoprotein cholesterol; Ultrasound — ultrasound examination.

The obtained data are compared with glycemic standards for healthy pregnant women. If the results of any two samples exceed the norm, the diagnosis of gestational diabetes mellitus (GDM) is confirmed. In the event of an inconclusive result—where the glycemic level exceeds the norm in only one of the four samples—the test is repeated after 2 weeks.

Recommended assessment plan for individuals with newly diagnosed type 2 diabetes mellitus

Given the clinical course of type 2 diabetes mellitus (T2DM), a specific assessment plan is recommended for individuals with a newly diagnosed condition (Table 2). Particular attention should be paid to the actual duration of the T2DM, the status of insulin resistance (IR), the functional state of pancreatic beta-cells, as well as the condition of the liver, kidneys, and cardiovascular system. C-peptide levels should be measured if the patient has previously been prescribed exogenous insulin. Testing for antibodies to glutamic acid decarboxylase (GAD antibodies) is advisable for individuals with normal or low body weight to facilitate differential diagnosis, specifically to rule out latent autoimmune diabetes in adults (LADA). It is also appropriate to assess vitamin B12 levels, as most patients will subsequently be prescribed metformin; at doses exceeding 1000 mg/day taken for more than 4 years, metformin can reduce blood levels of this vitamin (Ko S.-H. et al., 2014). The function of vitamin D is not limited solely to the regulation of calcium-phosphorus metabolism; it also influences other physiological processes in the body, including the modulation of cell growth, neuromuscular conduction, immunity, and inflammation. Currently, low serum vitamin D levels in patients with type 2 diabetes mellitus are considered a prognostic indicator for the subsequent development of macrovascular complications (Komisarenko Yu.I., 2015). At present, comprehensive examination and treatment for the majority of patients with diabetes mellitus can be fully managed in an outpatient setting—with the exception of patients presenting with severe manifestations of diabetic foot syndrome (such as trophic ulcers or gangrene) or chronic renal failure secondary to diabetic nephropathy, who require specialized instrumental, diagnostic, and therapeutic interventions. Improving the outpatient model of care for patients with diabetes mellitus will make it possible to reduce the number of dedicated inpatient beds.

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