Characteristics of glucose variability in different types of diabetes in young people

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Abstract: The article gives information about characteristics of glucose variability in different types of diabetes in young people.

Keywords: Diabetes mellitus, insulin, heterogenous disease, monogenic, MODY autoantibodies.

Introduction. Diabetes mellitus (DM) is a chronic heterogeneous disease caused by an absolute or relative deficiency of insulin, which initially causes disturbances in carbohydrate metabolism (CDM), and then in all types of metabolism, which ultimately leads to damage to all functional systems of the body [1]. All over the world, diabetes is getting younger and rapidly progressing; the onset of the disease is increasingly being diagnosed in patients under the age of 45 years. In addition, in the practice of an endocrinologist, it is not always possible to accurately identify the type of diabetes based on clinical signs, since rare monogenic forms of diabetes, which are the result of genetic mutations, can be diagnosed in this age group. According to various literature data, from 4 to 13% of cases of diabetes development in young people are caused by monogenic types [2, 3], which include adult-type diabetes in young people (Maturity Onset Diabetes of the Young - MODY), which differs in clinical picture (characterized by an autosomal dominant type of inheritance, manifestation at a young age and a mild course) and has features in the tactics of patient management.

The diagnosis of MODY should be suspected in young patients under 35 years of age with normal body weight, preserved β-cell secretion, absence of specific autoantibodies, and the presence of hyperglycemia in two or more generations among the proband's relatives [4, 5]. The most common types are MODY1, MODY2, MODY3, which account for 90% of identified cases [6]. Differential diagnosis of monogenic forms of diabetes is often difficult due to the lack of clear and pronounced differences from other types, as well as the small amount of information about this nosology from practicing physicians, which is dictated by the rarity of this type of

diabetes [7]. However, timely and accurate verification of the diagnosis has an impact on the choice of therapeutic tactics: from correction of NAD with a balanced diet to treatment with oral hypoglycemic drugs and insulin therapy [8].

Verification of MODY allows one to predict the course of diabetes: non-progressive, without the development of specific complications in MODY2 and, on the contrary, a pronounced decrease in β-cell function in MODY3 with the development of micro- and macrovascular complications. In addition, the diagnosis of MODY makes it possible to timely identify and predict the development of diabetes, and conduct medical and genetic counseling with relatives of patients. However, if the listed criteria are met, only 50% will have mutations leading to the development of MODY, which in some cases is due to the similarity of the clinical picture of MODY and type 2 diabetes (T2DM). This requires a more detailed study of the characteristics of the course and differential diagnostic criteria of MODY and is a relevant aspect in endocrinology.

Continuous glucose monitoring (CGM) has become increasingly popular over the past decade, providing information on ongoing trends in glucose levels to track diurnal changes and variability (CV), identify patterns of hypoglycemic conditions and hyperglycemia, and is an important diagnostic and educational tool. for patients with diabetes [9, 10]. Perhaps 24-hour glucose monitoring can become one of the tools that will help in the search for new characteristics of GV in young patients with diabetes.

Purpose of the study - to evaluate the characteristics of CH in different types of diabetes in young people using LMWH systems.

Materials and methods

*Object of study:*The 1st group consisted of 31 patients with a verified molecular genetic study of MODY2 (a pathogenic mutation in the glucokinase GCK gene was identified), the 2nd group included 16 patients with MODY3 (a pathogenic mutation in the hepatocyte nuclear factor HNF1A was identified). The comparison group was formed from patients with T2DM (25 people) who had no mutations in the GCK and HNF1A genes, as well as other MODY subtypes, no antibodies to insulin, β-cells, glutamate decarboxylase, and a normal level of C-peptide within 3 years from the onset of the disease. Thus, to study GV indicators in various types of diabetes in young people, three groups were formed: patients with GCKMODY (31 people), HNF1a-MODY (16 people) and T2DM (25 people). The groups are comparable by gender and age.

The examination of patients was carried out on the basis of the Samarkand State Medical University SFRSNPTSE. The clinical examination included: anamnesis (including family history) and a complete clinical examination of each patient: determination of body mass index, waist / hip size index, examination of the skin and

visible mucous membranes, palpation of the lymph nodes, auscultation of the lungs, heart and great vessels, determination swelling, palpation of the thyroid gland, abdomen. All patients were screened for diabetic complications within a year prior to examination.

To analyze GV, daily glucose monitoring was carried out for 14 days using the FreeStyle Libre system. The program automatically calculated glycemic profile indicators: average daily glycemic value, calculated level of glycated hemoglobin (HbA1c), time interval of the patient being in the target range, above and below it, glycemic variability. These indicators allow us to obtain more extensive information about carbohydrate metabolism in patients.

After LMWH, a graphical value of the glycemic level during the observation period was obtained. To convert graphic images into digital ones in order to determine the VG indices, mathematical data analysis is carried out. This requires the use of programs that automatically substitute data into mathematical formulas and calculate them. For the examined patient, graphical LMWH data in the form of a pdf file are transferred from the device to a personal computer and then reformatted in Microsoft Excel. Next, mathematical processing of the obtained data and calculation of VG indices is carried out. The results of the automatic calculation of GV indices are presented in the form of a report indicating the name of the index, its dimension, norm and values for a particular patient. For a more in-depth assessment of GV, the following indices were selected: average daily glycemic level (BG); standard deviation (SD); mean amplitude of glycemic fluctuations (MAGE); hyperglycemia risk index (HBGI); hypoglycemia risk index (LBGI). For the purpose of subsequent mathematical processing of the obtained data, calculating the GV indices selected for interpreting the results of this study, the specialized program GLINVA1 was used.

Statistical processing of the research results was carried out using the IBM SPSS Statistics 20.0 program. The nature of the distribution of quantitative characteristics was determined by the Kolmogorov-Smirnov method. In the case of a normal distribution, the mean value (M) and standard deviation (σ) were calculated. Data were presented as $M \pm \sigma$. When comparing two normally distributed samples, the Student's t-test was used. In the absence of a normal distribution, medians (Me) were calculated indicating the interquartile range - the 25th and 75th percentiles, and independent samples were compared using the Mann-Whitney test. Relationships between characteristics were assessed by calculating the Pearson linear correlation coefficient, and for interval and ordinal variables not subject to normal distribution, by the Spearman rank correlation coefficient. To determine the contingency of dichotomous variables, $\chi 2$ was used according to the Pearson or Fisher tests. In all statistical analysis procedures, the critical significance level of the null statistical hypothesis (p) was taken equal to 0.05.

Results. In the study groups there were 4 men with MODY3 (25.0%), MODY2 - 11 (35.5%, pMODY2-3 = 0.554), DM2 - 9 (36.0%, pMODY2-DM2 = 0.884, pMODY3-DM2 = 0.446); women with MODY3 - 12 (75.0%) (pMODY2-3 = 0.772), MODY2 - 20 (64.5%), DM2 - 16 (64.0%, pMODY2-DM2 = 0.921, pMODY3-DM2 = 0.561) . The median age of patients with MODY3 at diagnosis of hyperglycemia was 31.0 [18.0; 35.5] years; at MODY2 - 36.5 [18.0; 55.0] years (pMODY2-3 = 0.942), with T2DM - 28.0 [22.0; 36.0] years (pMODY2-DM2 = 0.095, pMODY3-DM2 = 0.081).

When studying the family history, it was determined that in persons with MODY3, 100% had carbohydrate metabolism disorders in 1st degree relatives, in persons with MODY2 - in 93.5% (29 people) (pMODY2-3 = 0.541), then as in T2DM - only in 54.5% (12 people) (pMODY2-DM2 = 0.002, pMODY3-DM2 = 0.002). Thus, when comparing aggravated family history according to NDU, it was determined that in MODY, hyperglycemia was detected more often in 1st degree relatives than in T2DM. These features of the hereditary history should be taken into account when carrying out the differential diagnosis of MODY and T2DM when collecting a family history of young patients with hyperglycemia.

The study measured HbA1c, fasting plasma glucose (FPG) and C-peptide. The level of C-peptide in T2DM was slightly higher than in other types of DM (Table 1). When studying the indicators of carbohydrate metabolism in individuals with different types of MODY, it was determined that with MODY2 the level of FPG (p = 0.003) and HbA1c (p = 0.001) was significantly lower than with MODY3. Individuals with mutations in the HNF1A gene had higher FPG and HbA1c values, in contrast to T2DM, although no significant differences were found.

Table 1.

Indicators of carbohydrate metabolism in MODY and type 2 diabetes mellitus, Me [25; 75]

Indicators (reference values)	MODY2	MODY3	T2DM	pMODY2-3	pMODY2-DM2	pMODY3-DM2
FPG (3.3-6.0), mmol/l	6.0 [5.8; 6.7]	7.1 [7.0; 8.0]	6.5 [5.7; 11.9]	0.003	0.367	0.590
HbA1c (<6.0), %	6.3 [6.0;6.5]	7.1 [6.8; 7.6]	6.4 [5.6;8.0]	0.001	0.068	0.590
C-peptide (0.7-1.9), ng/ml	0.8 [0.6;1.0]	0.8 [0.6;1.2]	1.0 [0.6; 1.3]	0.549	0.373	0.665

Note.MODY (Maturity Onset Diabetes of the Young) - adult-type diabetes mellitus in young people; T2DM - type 2 diabetes mellitus; FPG - fasting plasma glucose.

All patients with MODY and T2DM underwent 24-hour glucose monitoring with the FreeStyle Libre system for 14 days. The results obtained were analyzed. Estimated HbA1c levels were lower than those determined in the laboratory and were not significantly different. In MODY3, according to the results of LMWH, a more unfavorable profile was determined than in T2DM and MODY2 (Table 2). The time

patients spent in a state of hypoglycemia did not differ between individuals with MODY3 and T2DM. The median number of hypoglycemia and minutes of hypoglycemia also did not differ: for MODY3 they were 8.0 [0; 12.5] pieces of hypoglycemia and 76.0 [0; 192.3] min, with T2DM - 3.0 [0; 5.0] pieces (p = 0.193) and 71.0 [0; 177.0] min (p = 0.953), respectively. Thus, according to LMWH data, in MODY3 the daily level of glycemia is revealed to be higher than in T2DM and MODY2, which is comparable to the data on HbA1c determined in the laboratory.

Table 2.

Results of continuous glucose monitoring in patients with different types of diabetes mellitus, Me [25; 75]

Indicator (reference values), %	MODY2 (n = 31)	MODY3 (n = 16)	T2DM (n = 25)	pMODY2-3	pMODY2-DM2	pMODY3-DM2
Estimated HbA1c (<6.5)	6.3 [5.7; 7.0]	6.3 [5.7; 7.5]	5.8 [5.1; 6.3]	0.297	0.163	0.114
Glucose variability (<36)	17.1 [14.2; 20.5]	32.0 [27.6; 38.0]	25.5 [16.0; 31.9]	0.024	0.453	0.070
Time in target range (>70)	93.5 [71.7; 97.7]	75.0 [50.0; 87.0]	91.0 [64.5; 99.0]	0.318	0.974	0.266
Time above target range greater than 10.0 mmol/L (<25)	3.5 [2.8; 4.4]	8.0 [4.0; 36.0]	25.5 [16.0; 31.9]	0.426	0.002	0.135
Time less than target range less than 3.9 mmol/L (<4)	1.3 [0; 2.5]	2.0 [0; 7.0]	1.0 [0; 3.7]	0.478	0.650	0.935

Note. MODY (Maturity Onset Diabetes of the Young) - adult-type diabetes mellitus in young people; T2DM - type 2 diabetes mellitus, HbA1c - glycated hemoglobin.

When determining routine parameters of carbohydrate metabolism (FPG and HbA1c), most patients with MODY2 achieve target values. After performing LMWH and calculating GV indices, it is revealed that in some patients with mutations in the GCK gene, indices are higher than reference values, but lower than in other types of diabetes (Table 3). In individuals with MODY2, low GV is determined during the day, which probably causes a lower incidence of diabetic complications than in other types of diabetes.

Table 3.

Indicators of glucose variability in patients with different types of diabetes mellitus, Me [25; 75]

Glucose variability index (reference values), mmol/l	MODY2 (n = 31)	MODY3 (n = 16)	T2DM (n = 25)	pMODY2-3	pMODY2-DM2	pMODY3-DM2
BG (<5.6)	7.0 [6.4; 7.7]	6.9 [6.2; 9.6]	6.1 [4.9; 7.3]	0.397	0.253	0.369
MAGE (0-2.8)	2.5 [2.0; 2.8]	4.1 [2.3; 4.5]	2.1 [1.8; 3.7]	0.007	0.253	0.369
HBGI (0-7.7)	1.4 [0.9; 2.4]	3.5 [0.5; 7.3]	4.5 [2.6; 9.0]	0.017	0.001	0.812
LBGI (0-6.9)	0.7 [0.4; 1.1]	3.9 [1.3; 7.0]	0.7 [0.1; 6.1]	0.001	0.077	0.090
SD (0-2.8)	1.4 [1.2; 1.6]	2.6 [1.4; 2.8]	1.4 [1.1; 2.2]	0.001	0.155	0.127

Note. BG - average daily glucose level; HBGI (Hight Blood Glucose Index) - hyperglycemia risk index; LBGI (Low Blood Glucose Index) - hypoglycemia risk index; MAGE (Mean Amplitude of Glycemic Excurtion) - average amplitude of glycemic fluctuations; SD (Standard deviation) - degree of dispersion of glycemic

values; MODY (Maturity Onset Diabetes of the Young) - adult-type diabetes mellitus in young people; T2DM - type 2 diabetes mellitus.

Discussion

Differential diagnosis of the type of diabetes in young patients is difficult. Timely verification of diabetes has a significant impact on the choice of therapeutic tactics, predicting the course of the disease and the development of complications, as well as determining the risk of developing diabetes in relatives [11]. In their publication, scientists from the Russian National Research Medical University named after N.I. Pirogov, when identifying atypical clinical and laboratory manifestations of the disease in a patient, recommends analyzing the possibility of rare forms of diabetes, including MODY [12]. If the presence of MODY is suspected, in order to confirm the diagnosis, emphasis is placed on the need for genetic testing using AS 468 “Diabetes mellitus - hyperinsulinism” panel sequencing of 27 genes. In our work, the molecular genetic method was used to verify the type of diabetes. Of course, only this method allows you to accurately diagnose MODY [13]. However, the test is expensive and not available in routine clinical practice. In this regard, we set the goal of searching for new, more accessible methods and criteria for diagnosing monogenic forms of diabetes.

The advent of LMWH systems has led to an expansion of diagnostic capabilities. The introduction of technology into clinical practice made it possible to determine patterns and trends in changes in glucose levels and obtain reliable data on short-term glycemic control [14]. We determined that with an in-depth analysis of the glycemic profile using the LMWH method and calculations of GV indices, it is possible to assess the course of diabetes in young people and promptly determine patient management tactics. According to the results of our study, it was shown that in individuals with a mutation in the GCK gene, according to LMWH and analysis of GV indices, a favorable glycemic profile is determined, which corresponds to the results of a three-year study in which, when observing a group of patients with GCK-MODY, patients demonstrate a non-progressive course of this type Diabetes with stable indicators of carbohydrate metabolism and low fasting hyperglycemia persisting after 3 years [15].

Many researchers also note that MODY is often incorrectly diagnosed as T1DM or T2DM. The reason for this is not only clinical similarities with other types of diabetes, but also the high cost and limited access to genetic testing, as well as lack of awareness among clinicians. As a result of late diagnosis, patients do not receive appropriate effective treatment [16]. Therefore, one of the objectives of our study was to show the importance of timely diagnosis of rare types of diabetes. Previously, studies were carried out on the differential diagnosis of types of diabetes and it was noted that, despite recent data on the presence of non-immune forms of diabetes in

childhood, the absolute majority of children with diabetes have type 1 diabetes [17]. In pediatrics, problems arise when identifying low-grade hyperglycemia, often detected by chance, in the absence of clinical manifestations, when we are talking about early diagnosis of T1DM or a mild manifestation of the disease, characteristic of T2DM or MODY. In our study, the main group included persons over 18 years of age, however, timely diagnosis in the proband makes it possible to examine close relatives and determine the disease in them. According to the results of our scientific work, it was shown that in patients with MODY, 100% of patients with MODY were identified with first-degree relatives.

Of course, T1DM and T2DM prevail among patients with this nosology. In accordance with Russian clinical guidelines for diabetes, the use of LMWH technology in patients with T1DM and T2DM is recommended to achieve individual targets for glycemic control, reduce the risk of hypoglycemia (including severe) and GV, increase time in the target range, and improve quality of life [18, 19]. Portable LMWH systems and GV analysis are actively used for patients with these types of diabetes. Thus, in 2022, a study (n = 400) was conducted in Novosibirsk in patients with T1DM from 18 to 65 years of age on basal-bolus insulin therapy, during which GV indices were calculated at night and during the day according to LMWH data [20]. The authors justify their scientific work by the fact that GV is recognized as a risk factor for vascular complications of diabetes and hypoglycemia, pointing to the fact that currently little is known about the factors influencing GV in patients with diabetes. However, it is extremely important to suspect rare types of diabetes, which MODY belongs to, in time and determine the correct treatment tactics. This aspect is of high importance not only in endocrinology, but also in obstetrics when managing pregnancy in patients with MODY. In this regard, it is necessary to develop guidelines for the management of women with MODY during pregnancy and in the early postpartum period [21]. Finding criteria for screening for MODY will greatly facilitate the work of genetic laboratories. In addition, it is necessary to develop and implement training programs for doctors and patients on the use of LMWH devices, as well as the interpretation of data obtained from LMWH [22].

Conclusion

Currently, approaches to managing diabetes should include not only glycemic control, but also minimizing the risks of complications and reducing daily GV, since high GV is an independent risk factor for complications of diabetes. Therefore, indicators such as the therapeutic target are important for patients with different types of diabetes. Using LMWH in the management of young people with various types of diabetes, we can conduct an in-depth analysis of VG and adjust treatment, helping to reduce the risk of complications of diabetes and improve the quality of life of patients.

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