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ХАРАКТЕРИСТИКИ ВАРИАБЕЛЬНОСТИ ГЛЮКОЗЫ У ПАЦИЕНТОВ С GCK-MODY

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Characteristics of Glycemic Variability in Patients with GCK-MODY

Резюме

GCK-MODY — один из самых распространённых вариантов сахарного диабета (СД) типа MODY (40–60 %) в европейской популяции. При диагностировании GCK-MODY возможно использование систем непрерывного мониторинга глюкозы (НМГ), что позволяет проводить углубленный анализ вариабельности глюкозы (ВГ) с использованием математических индексов и детально оценивать гликемический профиль. Цель исследования — изучить особенности вариабельности уровня глюкозы у лиц молодого возраста с GCK-MODY диабетом. У 20 пациентов (7 мужчин и 13 женщин, медиана возраста при диагностировании СД была 28,0 [18,0; 36,0] лет) с подтвержденной молекулярно-генетическим исследованием мутацией в гене глюкокиназы проведено суточное исследование уровня глюкозы с использованием портативных систем НМГ и анализ индексов вариабельности глюкозы с помощью специализированной компьютерной программы GLINVA.

При определении рутинных показателей углеводного обмена (глюкозы плазмы натощак (ГПН) и гликированного гемоглобина) у большинства пациентов с GCK-MODY наблюдаются целевые значения, что определяет тактику ведения пациентов из данной группы пациентов (рациональное питание или минимальные дозы пероральных сахароснижающих препаратов). Однако после проведения НМГ и изучения индексов ВГ, определено, что у некоторых пациентов индексы были выше референсных значений при нормальных показателях гликированного гемоглобина и ГПН, что требует коррекции терапии. Полученные результаты при изучении ВГ у лиц с GCK-MODY показывают низкую ВГ в течение суток, что, вероятно, обуславливает меньшую частоту развития диабетических осложнений и определяет тактику ведения пациентов.

Ключевые слова: *GCK-MODY диабет, вариабельность глюкозы, непрерывный мониторинг глюкозы*

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Abstract

GCK-MODY is one of the most common MODY variants (40–60 %) in the European population. It is possible to use continuous glucose monitoring systems (CGMS) when diagnosing GCK-MODY which allows for an analysis of glucose variability (GV) using mathematical indices and a detailed assessment of the glycemic profile. The purpose of this abstract is to investigate the features of GV in young people with GCK-MODY. A daily study of glucose levels was performed using portable systems for CGMS in 20 patients (7 men and 13 women, median age at diagnosis of DM was 28.0 [18.0; 36.0] years) with a mutation in the glucokinase gene confirmed by molecular genetic testing. There was also performed an analysis of glycemic variability indices with the specialized GLINVA program.

Most patients with GCK-MODY have target values when determining routine indicators of carbohydrate metabolism (fasting plasma glucose (FPG) and glycated hemoglobin), they determines the tactics of managing patients from this group of patients (rational nutrition or minimal doses of oral hypoglycemic drugs). However, after conducting CGMS and studying the GV indices it was determined that in some patients the indices were higher than the reference values with normal levels of glycated hemoglobin and FPG, and it is this group of patients that needs therapy correction. The results demonstrate a flat glycemic profile during the day which probably causes a lower incidence of diabetic complications and determines the tactics of GCK-MODY patient management.

Key words: *GCK-MODY, glycemic variability, continuous glucose monitoring*

Conflict of interests

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BG — average daily blood glucose level, CGM — continuous glucose monitoring, CMD — carbohydrate metabolism disorders, DM — diabetes mellitus, FPG — fasting plasma glucose, GAD — anti-glutamic acid decarboxylase autoantibody, GCK — glucokinase, GV — glucose variability, HbA1c — glycated hemoglobin, HBGI — high blood glucose index, IA-2A — antibodies to tyrosine phosphatase, ICA — islet-cell antibodies, LBGI — low blood glucose index, MAGE — mean amplitude of glycemic excursion, MODY — maturity-onset diabetes of the young, NGS — next generation sequencing, OHGD — oral hypoglycemic drugs, SD — standard deviation

Introduction

GCK-MODY (Glucokinase-maturity-onset diabetes of the young) is one of the most common variants (40–60 %) of MODY-type diabetes mellitus (DM) in the European population [1]. Most patients diagnosed with GCK-MODY demonstrate no clinical manifestations of diabetes mellitus (DM), and carbohydrate metabolism disorders (CMD) in such cases are found during routine tests [2]. Hyperglycemia associated with glucokinase defects is usually moderate and may be either intermittent or stable over months, or even years. The severity of fasting hyperglycemia in GCK-MODY patients increases very slowly; glycated hemoglobin (HbA1c) level varies from 5.9 % to 7.6 % [3, 4].

When diagnosing GCK-MODY, continuous glucose monitoring (CGM) systems can be used; they allow performing a comprehensive analysis of glucose variability (GV) using mathematical indices, as well as detailed assessment of glycemic profile [5]. These measures help to determine the most optimal and effective approach for managing such patients, since they do not always require insulin therapy and oral hypoglycemic drugs (OHGD); in most cases, dietary recommendations are sufficient. Moreover, using the CGM technique in the proband's relatives allows diagnosing them with carbohydrate metabolism disorders at preclinical stages, predicting the course of the disease, and prescribing a pathogenetic therapy. Thus, modern diagnostic methods can help to reduce the rate of medical errors in the diagnosis and management of patients with such a rare type of DM as GCK-MODY; it improves their life quality and is an important issue in endocrinological practice.

The objective of this study was to analyze the specific features of glucose variability in young patients with GCK-MODY diabetes mellitus.

Materials and methods

The study was performed at the Research Institute for Treatment and Preventive Medicine (RITPM), a branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (C&G SB RAS). At the first stage of the study, the patients (n = 66) who were previously observed with a diagnosis of "diabetes mellitus, type to be clarified, possibly MODY" underwent a complete clinical examination; the following parameters of carbohydrate metabolism were assessed: fasting plasma glucose (FPG), C-peptide, HbA1c level and antibodies (to pancreatic β-cells, to glutamate decarboxylase, to tyrosine phosphatase). Criteria for inclusion in the group of patients with GCK-MODY phenotypic signs: age of hyperglycemia diagnosis from 18 to 45 years; signed informed consent to participate in the study; carbohydrate metabolism disorder, twice confirmed by laboratory test results (DM diagnosis was verified on the basis of two laboratory tests of fasting blood glucose ≥ 6.1 mmol/L for whole capillary blood (7.0 mmol/L for venous plasma) and/or 2 hours after oral glucose tolerance test, or random determination of glucose in whole capillary or venous blood ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5 %;); no antibodies to pancreatic β-cells (ICA), glutamate decarboxylase (GAD), tyrosine phosphatase (IA-2A); normal or slightly reduced C-peptide level; no absolute need for insulin therapy; no ketoacidosis at the time of disease onset. Exclusion criteria: history of tuberculosis of lungs or other organs; history of human immunodeficiency virus infection; present infectious disease due to hepatitis B virus or hepatitis C virus that requires antiviral treatment; administration drug products that cause hyperglycemia, including glucocorticoids; confirmed neonatal diabetes mellitus in the proband; phenotypic signs of other genetic syndromes in the proband, with the symptom complex including hyperglycemia.

At the next stage, all patients underwent molecular genetic analysis using targeted high-throughput next-generation sequencing (NGS) technique. The mutations found were verified using direct automated Sanger sequencing. According to the study results, GCK-MODY was confirmed in 43 (65.1 %) out of 66 examined patients. To study glucose variability in young patients with GCK-MODY diabetes mellitus, a random sample of 20 patients (7 male and 13 female patients, median age at the time of being diagnosed with DM was 28.0 [18.0; 36.0]) was selected. Median DM duration was 2.0 [1.0;4.0] years. Baseline parameters of the studied group of patients are presented in Table 1.

At the time of enrollment, patients had no overweight or obesity, cardiovascular diseases, diabetic retinopathy, or nephropathy.

At the third stage, the studied group of patients received a CGM system — portable Medtronic MiniMed (USA). For the study, the portable systems in each patient were programmed to measure glucose level every 5 minutes for at least 5 days. The median CGM duration was 6.0 [5.0; 13.0] days. The monitoring results were integrated into the Medtronic CareLink®Pro software. To analyze GV, the following values were assessed: average daily glucose level (BG, blood glucose), standard deviation (SD), mean amplitude of glycemic excursion (MAGE), high blood glucose index (HBGI), low blood glucose index (LBGI). For the subsequent mathematical processing of the data obtained and for the calculation of GV parameters selected for interpreting

Table 1. *Characteristics of patients with GCK-MODY (n=20)*

Indicators (reference values), units of measurement	Index (median)
Gender	65.0 % female patients; 35.0 % male patients (p = 0.08)
The average age of diagnosis verification, years	28,0 [18,0; 36,0]
The median duration of diabetes, years	2,0 [1,0;4,0]
FPG (3,3–6,0), mmol/l	6,1 [5,8; 7,0]
HbA1c (less than 6.5), %	6,0 [4,5;6,6]
C-peptide (0.7–1.9), ng/m	0, 8 [0,4;1,7]
Body mass index (weight, kg/height, m^2)	28,3 [21,7; 29,4]
LDL-C, mmol/l	2 [1,7;2,9]
HDL-C, mmol / l	1,3 [1,0;1,4]
Общий холестерин, ммоль/л/ Total cholesterol, mmol/l	4,5 [4,3;5,1]
Триглицериды, ммоль/л/ Triglycerides, mmol/l	1,2 [1,0;1,5]
Отягощенный анамнез по ССЗ/ Burdened history of CVD, n (%)	4 (20,0)
Отягощенный анамнез по СД/ Burdened history of diabetes, n (%)	2 (10,0)
Курение/ Smoking, n (%)	7 (35,0)

Примечание: данные приведены как Me (25-й процентиль — 75-й процентиль), n (%); ГПН — глюкоза плазмы натощак; СД-сахарный диабет; ССЗ-сердечно-сосудистые заболевания; ЛПВП — липопротеиды высокой плотности; ЛПНП-липопротеиды низкой плотности
Note: data are given as Me (25th — 75th percentile); FPG — fasting plasma glucose; CVD — cardiovascular disease; LDL -C — low density lipoproteins; HDL-C — high density lipoproteins

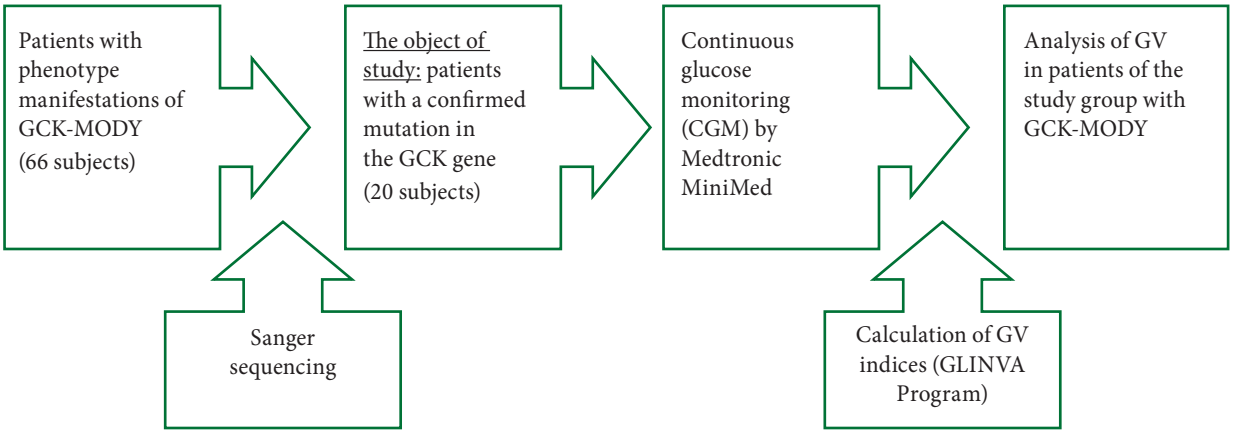

Figure 1. *Research design*
Note: GCK gene — Glucokinase gene, CGM — Continuous glucose monitoring, GV — Glycemic Variability, GCK -MODY — Glucokinase maturity onset diabetes of the young

the results of this study, a specialized calculator software GLINVA (Russia) was used. The GLINVA calculator software was developed at RITPM, a branch of the C&G SB RAS (computer software state registration certificate No. 2019660636 dated August 9, 2019; patent for an invention No. 2746830 dated April 21, 2021). The design of this study is provided in Figure 1.

Statistical processing of the results was carried out using IBM SPSS Statistic 23 software (USA). Since the distribution of quantitative characteristics differed from the normal one, non-parametric methods of analysis were used: median (Me) was determined, with the 25th and the 75th percentiles in the Me format [Q25; Q75].

Results and discussion

The results of the study revealed that most patients (19; 97.0 %) with GCK-MODY achieved the target levels of FPG and HbA1c (Table 2). C-peptide median level was within the reference values in 100.0 % of cases; it indicates the preserved insulin secretion by pancreatic b-cells. GV parameters were assessed in all patients of the studied group; the results are presented in Table 2; one can compare the values in individuals with no DM and in GCK-MODY patients.

The SD parameter is used in many research papers and describes the dispersion of glycemic values. Mean daily glucose (BG, blood glucose) is calculated automatically by the CGM system; in this study it was 7.5 mmol/L that confirms mild hyperglycemia in GCK-MODY patients. The MAGE score was developed to assess postprandial hyperglycemia. In individuals with normoglycemia, this value ranges from 0 to 2.8 mmol/L. Similar values were observed in patients with GCK-MODY; it indicates low GV and is probably associated with a low risk of micro- and macrovascular complications. The risks of hypo/hyperglycemia can be assessed by calculating HBGI (hyperglycemia risk) and LBGI (hypoglycemia risk). In GCK-MODY patients, the risk of hyperglycemia is within the reference range, as well as in individuals with normoglycemia. The increased LGBI value indicates the possibility of hypoglycemia in the studied group. Analysis of the CGM curves of all 20 patients revealed that they had no nighttime (00:00–06:00) hypoglycemia episodes. Based on the data obtained, it was found that even individuals with GCK-MODY who have achieved the target levels of FPN and HbA1c require CGM to determine the indications for treatment adjustment.

There are few published data on the CGM in individuals with MODY. In 2017, Moscow researchers conducted a similar study with 312 patients (162 male, 150 female patients) aged from 3 months to 25 years, suspected of MODY [6]. It was found that the most

Table 2. *Indicators of glycemic variability in patients with GCK-MODY (n=20)*

Different Indexes of Glycemic Variability (M)	Reference values of GV parameters in individuals without DM	GV scores in individuals with GCK-MODY
BG (blood glucose), mmol/l	<5,6	7,5
MAGE (mean amplitude of glycemic excursions), mmol/l	0 — 2,8	2,5
HBGI (high blood glucose index)	0 — 7,7	1,6
LBGI (low blood glucose index)	0 — 6,9	9,0
SD (standard deviation)	0 — 2,8	1,5

Note: GV — glucose variability, DM — diabetes mellitus

common MODY subtype in the Russian population is GCK-MODY. According to the results of our study, GCK-MODY was confirmed in 65.1 % of the subjects. Median glycated hemoglobin in the above work was 6.4 [4.5; 7.7] %; it did not differ from the median HbA1c level at the time of diagnosis that indicates a non-progressive course of carbohydrate metabolism disorders in GCK-MODY. One of the typical signs of the studied diabetes type is the moderate fasting hyperglycemia. All patients had fasting hyperglycemia at the time of CMD detection, and it is comparable to the results of our study.

The results of scientific studies revealed that, despite a long history of hyperglycemia in patients (the mean duration was 48.6 years) with mutations in GCK gene, the prevalence of micro- and macrovascular diabetic complications in them was the same as in the general population [7; 8]. The risk of developing cardiovascular diseases (CVD) in individuals with GCK-MODY is similar to the population risk [9]. Some other studies provide similar data, that although β-cell and hepatocyte function in GCK-MODY is altered, hyperglycemia associated with glucokinase defects is usually moderate. Nevertheless, mutation carriers have CMD since birth [10]; they can be detected as early as in the first years of life and, in almost all individuals, by the end of sexual maturation [11]. The severity of fasting hyperglycemia increases very slowly: HbA1c level in patients with GCK-MODY is 5.9–7.3 % in the age group up to 40 years, and 5.9–7.6 % in the age group 40+. A more aggressive course of this type of DM is observed in cases when a GCK mutation is accompanied by insulin resistance and obesity [7].

Turkish scientists performed glucose level monitoring in 8 patients with mutations in the *GCK* gene with a glycated hemoglobin level of up to 7 %. They found that daily glucose values were above the normal range in half of patients. Thus, the individuals with GCK-MODY do not present high glucose levels, however, they should be adjusted with dietary and lifestyle changes [12]. The results of this study are consistent with the data obtained during the research work in our clinic; they demonstrate the reasonability of dietary interventions and hypoglycemic therapy for individuals with GCK-MODY, since several patients do not achieve their target values. Thus, the assessment of glucose variability using modern portable systems has been successfully used to analyze the course of a monogenic type of diabetes mellitus.

Conclusion

1) Most patients with GCK-MODY had target values of the routine carbohydrate metabolism (FPG and HbA1c) parameters, however, CGM results revealed that the values in several patients are higher than the reference ones; therefore, the treatment should be adjusted.

2) The patients with GCK-MODY had low daily glucose variability that probably causes a lower frequency of diabetic complications than in the patients with other DM types.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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