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DEFINITION OF THE DEPENDENCE OF QTc INTERVAL PROLONGATION ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Ключевые слова: *сахарный диабет 2 типа, интервал QTc, вариабельность гликемии*

Abstract. **Definition of the dependence of QTc interval prolongation on glycemic control in patients with type 2 diabetes mellitus.** *Pertseva N.O., Moshenets K.I. The aim of the study: to assess the impact of glycemic variability on the duration of QTc interval in patients with diabetes mellitus type 2. 68 patients with type 2 diabetes mellitus (DM) and glycosylated hemoglobin (HbA1c) level $\leq 10\%$ were examined. Of them – 37 (54.4%) men and 31 (45.6%) women. The average age – 46.0 (43.0; 54.0) years, the duration of DM type 2 – 7.0 (5.0; 9.0) years. Patients were divided into 2 groups according to HbA1c level: group 1 (n=31) with HbA1c $< 7\%$ and group 2 (n=37) with HbA1c $\geq 7\%$. The control group consisted of 10 practically healthy people, compared by gender and age. The duration of the QTc interval was calculated automatically by Bazett's formula during 24-hour Holter electrocardiogram (ECG) recordings. Additionally, the percentage of cases of exceeding the QTc threshold over 450 ms ($QTc > 450$) was also calculated. Simultaneously with 24-hour Holter monitoring, the continuous glucose monitoring was performed, using iPro2 system (Medtronic MiniMed, USA). The maximum value of glycemia (Gmax), the minimum value of glycemia (Gmin), as well as indicators*

of glycemia variability (GV) were analyzed: standard deviation of mean glycemia (SD) and glycemia range (GR). The duration of daily QTc and the value of QTc >450 in patients with type 2 DM were significantly greater compared with the control group ($p < 0.05$) and did not depend on the HbA1c level. In type 2 DM patients without recorded hypoglycemic episodes, the characteristics of QTc did not differ from the results of the control group ($p > 0.05$). At the time of the hypoglycemic episode, the QTc duration in patients with type 2 DM significantly increased compared with the average daily value of QTc in the same patients – 487 (466; 519.5) ms against 436.5 (431; 452) ms ($p < 0.001$). A strong correlation between QTc duration and the presence of hypoglycemia was determined ($r_s = 0.78$; $p = 0.023$). QTc duration also correlated with GR ($r_s = 0.23$; $p = 0.016$) and SD ($r_s = 0.21$; $p = 0.021$). Therefore, it was found that in patients with type 2 diabetes, the prolongation of QTc duration is associated with high glycemic fluctuations and hypoglycemia ($p < 0.05$) regardless of the HbA1c level.

Реферат. Визначення залежності подовження інтервалу QTc від контролю глікемії у хворих на цукровий діабет 2 типу. Перцева Н.О., Мошенець К.І. Мета дослідження – оцінити вплив варіабельності глікемії на тривалість інтервалу QTc у хворих на цукровий діабет 2 типу. Обстежено 68 хворих на цукровий діабет (ЦД) 2 типу з рівнем глікозильованого гемоглобіну (HbA1c) $\leq 10\%$. З них – 37 (54,4%) чоловіків та 31 (45,6%) жінка. Середній вік хворих – 46,0 (43,0; 54,0) років, тривалість ЦД 2 типу – 7,0 (5,0; 9,0) років. Пацієнти були розподілені на 2 групи за рівнем HbA1c: група 1 ($n=31$) з HbA1c $< 7\%$ та група 2 ($n=37$) з HbA1c $\geq 7\%$. Група контролю включала 10 практично здорових людей, порівняних за статеві-віковими характеристиками. Визначення тривалості інтервалу QTc відбувалось автоматично за формулою Bazett під час аналізу 24-годинного запису холтерівського моніторингу електрокардіограми (ЕКГ). Додатково визначали відсоток випадків перевищення порогу QTc більше 450 мс (QTc > 450). Одночасно з холтерівським моніторингом ЕКГ виконувалось тривале моніторування глікемії за системою iPro2 (Medtronic MiniMed, USA). Аналізувались максимальне значення глікемії (Гмакс), мінімальне значення глікемії (Гмін), а також показники варіабельності глікемії (ВГ): стандартне відхилення середньої глікемії (SD) та розмах глікемії (РГ). Тривалість добового QTc та показник QTc > 450 у хворих на ЦД 2 типу були значуще більшими порівняно з групою контролю ($p < 0,05$) і не залежали від рівня HbA1c. У хворих на ЦД 2 типу без зафіксованих гіпоглікемічних епізодів характеристики QTc не відрізнялись від результатів у контрольній групі ($p > 0,05$). На момент гіпоглікемічного епізоду тривалість QTc хворих на ЦД 2 типу суттєво зростала порівняно із середньодобовим значенням QTc у цих же хворих – 487 (466; 519,5) мс проти 436,5 (431; 452) мс ($p < 0,001$). Установлено сильний кореляційний зв'язок тривалості QTc з наявністю гіпоглікемії ($r_s = 0,78$; $p = 0,023$). Також тривалість QTc корелювала з РГ ($r_s = 0,23$; $p = 0,016$) та SD ($r_s = 0,21$; $p = 0,021$). Отже визначено, що у хворих на ЦД 2 типу незалежно від рівня HbA1c подовження QTc зумовлюється високими коливаннями глікемії та гіпоглікемією ($p < 0,05$).

The high frequency of cardiovascular complications in patients with type 2 diabetes mellitus (DM) significantly reduces the quality of life, leads to early disability and high mortality [9].

The QT interval reflects the duration of myocardial depolarization and repolarization processes. Prolonged QT duration is associated with an increased risk of cardiovascular and all-cause mortality in both the general population and patients with DM [8].

The duration of the QT interval depends on the heart rate (HR), so to estimate the time of myocardial repolarization not an absolute but a corrected value of the QT interval (QTc) is used. To calculate the duration of QTc, there are several correction formulas: Bazett, Fridericia, Framingham, Hodges, Rautaharju. In clinical trials, the vast majority use the Bazett formula, but it has certain limitations, namely: the possibility of its use at a HR in the range of 60-100 beats per minute [6].

In the literature many patient-specific risk factors for QTc prolongation is mentioned, namely: female gender, age over 65 years, cardiovascular history, family history of sudden cardiac death, hepatic and

renal failure, electrolyte disturbances. It is emphasized that in an individual this risk increases with increasing number of these risk factors. Clinically, the syndrome of prolonged QT may be manifested by episodes of syncopal states caused by attacks of specific polymorphic ventricular tachycardia such as torsade de pointes, the danger of which is due to the possibility of transition to ventricular fibrillation [5].

Due to the proven relationship between the duration of the QT interval and the occurrence of sudden cardiac death, in many works the authors suggest the possibility of using its duration as a rapid and objective method to determine the category of patients at high risk of cardiovascular events [10].

The prevalence of prolonged QT interval in patients with type 2 DM reaches 30%. The presence of DM in a patient already causes a high or very high cardiovascular risk. Accordingly, if such a patient is diagnosed with prolongation of the QT interval, he needs special attention to prevent the occurrence of fatal cardiovascular events [8, 10].

In existing studies on the QT interval in patients with type 2 DM the role of microvascular complications, systolic blood pressure, coronary heart disease

and cardiac autonomic neuropathy as additional factors that increase its duration has been proven. At the same time, isolated studies on the effect of actual blood glucose levels on the duration of the QT interval in patients with type 2 diabetes have shown disputable results [2, 15].

The aim: to assess the impact of glucose variability on the duration of QTc interval in patients with diabetes mellitus type 2.

MATERIALS AND METHODS OF RESEARCH

We examined 68 patients with type 2 DM with different glycemic control examined, of them – 37 (54.4%) men and 31 (45.6%) women. The average age of patients was 46.0 (43.0; 54.0) years, the duration of type 2 diabetes was 7.0 (5.0; 9.0) years. All patients were on combination antihyperglycemic therapy. 59 (86.8%) patients received double therapy and 9 (13.2%) patients received triple therapy: combination therapy with biguanides (metformin) and sulfonylureas – 18 (26.5%) patients; biguanides + sodium-glucose cotransporter 2 (SGLT2) inhibitors – 11 (16.2%) patients; biguanides + dipeptidyl peptidase-4 (DPP-4) inhibitors – 2 (2.9%) patients; biguanides + glucagon-like peptide 1 (GLP-1) analogues – 6 (8.8%) patients; biguanides + long-acting insulin analogues – 13 (19.1%) patients; biguanides + human isophane insulins – 9 (13.2%) patients; biguanides + SGLT2 inhibitors + long-acting insulin analogues – 5 (7.4%) patients; biguanides + sulfonylureas + DPP-4 inhibitors – 1 (1.5%) patient; biguanides + GLP-1 analogues + long-acting insulin analogues – 3 (4.4%) patients.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects.

Inclusion criteria: patients with type 2 diabetes aged ≥ 18 years to 65 years with the level of glycosylated hemoglobin (HbA1c) ≤ 10 %.

Exclusion criteria: acute diabetic complications at the time of inclusion; heart failure III, IV according to the classification of the New York Heart Association (NYHA); uncontrolled hypertension; congenital and acquired heart defects; atrial fibrillation; HR < 60 beats and > 100 beats per minute; coronary heart disease; history of myocarditis; cardiomyopathy; suffered acute cerebrovascular accident and transient ischemic attack; electrolyte imbalance; disorder of the automatism of the sinus node and conduction; use of drugs that lead to QTc prolongation (antiarrhythmics, antipsychotics, antidepressants, diuretics, antibiotics, systemic antifungals); period of exacerbation of concomitant chronic pathology, glomerular filtration rate < 45 ml/min., pregnancy, liver failure, family history of sudden death.

The state of carbohydrate metabolism was determined by the level of HbA1c and the results of continuous glucose monitoring (CGM).

HbA1c was determined by immunoturbidimetry using an automatic biochemical analyzer "SAPPHIRE 400" (Tokio Boeki, Japan, 2009) according to the National Glycohemoglobin Standardization Program (NGSP). HbA1c reference values: 4.5-6.5%.

For CGM the iPro2 GMS system (Medtronic MiniMed, USA) was used, followed by processing using CareLink iPro system. The maximum value of glycemia (Gmax), the minimum value of glycemia (Gmin), as well as indicators of glucose variability (GV) were analyzed: standard deviation of mean glycemia (SD) and glycemia range (GR). Hypoglycemia was considered at a blood glucose level to be < 3.9 [2].

Simultaneously with the CGM, Holter monitoring of the electrocardiogram (ECG) was performed for 24 hours on a blood pressure monitor and electrocardiographic signals SDM23 (manufacturer: X-Techno Ukraine).

QTc duration was calculated automatically according to the Bazett formula using ARNIKA software version 8.3.9.

$QTc = \text{measured QT} / \sqrt{\text{interval RR}}$.

The percentage of cases of exceeding the QTc threshold over 450 ms ($QTc > 450$) was also calculated.

Patients were divided into 2 groups according to the level of HbA1c: group 1 (n=31) of optimal glycemic control with HbA1c $< 7\%$ and group 2 (n=37) of insufficient glycemic control with HbA1c $\geq 7\%$.

The control group included 10 practically healthy people, compared by gender and age.

Statistical processing of the study results was performed using biostatistics methods implemented in Microsoft Excel software packages (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 (StatSoftInc., Serial № AGAR909E415822FA). The hypothesis of the normality of the distribution among the studied quantitative traits was tested according to the Shapiro-Wilk test (SW-W), and the equality of variances was tested using the Levin test.

The distribution of mostly all quantitative variables in almost all groups did not correspond to the normal law, so the median and interquartile range of Me (25%; 75%) were used to describe the central trend of continuous data. Relative (%) values were calculated to describe qualitative characteristics. In order to analyze the relationships between the studied traits, a correlation analysis was performed with the calculation of Spearman's rank correlation coefficients (r_s). The correlation coefficient in the range of $0.7 \leq |r_s| < 1$ indicated a strong correlation;

$0.3 \leq |r_s| < 0.7$ – on the connection of medium strength; $0 < |r_s| < 0.3$ – for a weak correlation [1].

RESULTS AND DISCUSSION

The duration of daily QTc and the value of QTc >450 in patients with type 2 DM were significantly greater compared with the control group ($p < 0.05$) and did not depend on the level of HbA1c and gender (Table 1).

A detailed analysis of QTc characteristics in groups of 2 DM patients based on their gender also revealed a significant prolongation of the daily QTc interval and an increase in QTc > 450 compared to a gender-

matched control group ($p < 0.05$), without significant differences between groups 1 and 2 (Table 2).

When assessing the characteristics of glycemia, it was found that patients with type 2 DM had significantly higher SD, Gmax, GR values compared to the control group ($p < 0.05$) and only the Gmin value did not differ from the control ones. Groups 1 and 2 were comparable in terms of Gmin and SD characteristics ($p > 0.05$). The group of insufficient glycemic control had significantly higher Gmax and GR compared to the group of optimal control ($p < 0.05$) (Table 3).

Table 1

Daily characteristics of the QTc interval in groups of patients with type 2 diabetes and in the control group (median and interquartile range Me (25%; 75%))

Values	Group 1 (n=31)	Group 2 (n=37)	Control (n=10)
QTc daily (ms)	436 (431; 445)*	438 (428; 447)*	420 (413; 433)
QTc >450 (%)	16 (7; 27)*	17 (9; 30)*	8.5 (6; 10)

Note. * – $p < 0.05$ compared to control.

Hypoglycemia was determined in 10 (32.25%) patients of group 1, in 12 (32.43%) patients of group 2, in general in 22 (32.35%) patients with type 2 diabetes. Differences between groups of patients did not reach the level of statistical significance ($p > 0.05$).

Further, the QTc duration characteristics were analyzed within each group of patients with type 2 DM depending on the presence of registered hypo-

glycemia in CGM, regardless of their gender. In group 1, the duration of QTc in patients with hypoglycemia was 445 (439; 472) ms, which was significantly longer than the control – 420 (413; 433) ms ($p = 0.029$). QTc >450 ms was also higher in patients with type 2 DM of the optimal control group in the case of a fixed hypoglycemic episode compared with the control – 24 (12; 29)% vs. 8.5 (6; 10)% ($p = 0.014$).

Table 2

Daily characteristics of the QTc interval in groups of patients with type 2 diabetes and in the control group, considering gender (median and interquartile range Me (25%; 75%))

Values	Group 1 (n=31)		Group 2 (n=37)		Control (n=10)	
	men (17)	women (14)	men (20)	women (17)	men (5)	women (5)
QTc daily (ms)	435 (429; 441)*	437 (430; 445)*	437 (425; 446)*	439 (428; 450)*	420 (410; 433)	421 (413; 434)
QTc >450 (%)	15 (7; 25)*	16 (7; 28)*	16 (8; 29)*	17 (9; 32)*	7.5 (5; 9)	9 (7; 10)

Note. * – $p < 0.05$ compared to control.

At the same time, the characteristics of the QTc interval of patients with optimal glycemic control without recorded hypoglycemic episodes did not

differ from the values of control group ($p > 0.05$). Therefore, in the group of patients with type 2 DM with optimal glycemic control QTc was 436 (431;

445) ms per day against 421 (415; 436) ms those of without hypoglycemia ($p=0.021$). QTc >450 ms in patients with hypoglycemia group 1 – 24 (12; 29)% against 9 (5; 13)% in those of without hypoglycemia ($p=0.001$).

In group 2, similar to group 1, the duration of QTc per day was 438 (428; 449) ms and was significantly longer compared to the control group ($p=0.036$). The duration of daily QTc in patients of group 2 with hypoglycemia was 448 (431; 496) ms against 425 (417; 439) ms in those of group 2

without hypoglycemia ($p=0.001$). QTc >450 ms exceeded control values: 17 (9; 31) % vs. 8.5 (6; 10)% ($p=0.023$) and this was due to patients of group 2 with hypoglycemia – 28 (14; 36)% ($p=0.001$), while in patients of this group without hypoglycemia its value was 9.5 (6; 13)% and did not differ from the control group ($p>0.05$). Patients in the group of insufficient glycemic control without recorded hypoglycemia during CGM had no differences in this value compared to the control ($p>0.05$) (Table 4).

Table 3

Characteristics of glycemia in groups of patients with diabetes mellitus type 2 and in the control group (median and interquartile range Me) (25%; 75%)

Values	Group 1 (n=31)	Group 2 (n=37)	Control (n=10)
SD (mmol/L)	2.5 (2.1; 2.8)*	2.8 (1.7; 3.8)*	0.9 (0.7; 1)
Gmin (mmol/L)	3.9 (3.6; 4.8)	5.1 (3.8; 6.8)	4 (3.9; 4.1)
Gmax (mmol/L)	10.1 (8.9; 12)*	13.9 (12; 16.6)*#	7.5 (7.2; 7.6)
GR (mmol/L)	8.3 (4.1; 9.4)*	11.4 (4.8; 10.1)*#	3.5 (3.2; 3.6)

Notes: 1. * – $p<0,05$ compared to control; 2. # – $p<0,05$ between groups of patients with type 2 DM.

At the time of the hypoglycemic episode, the QTc duration in patients with type 2 DM significantly increased compared with the average daily value of QTc in the same patients – 487 (466; 519.5) ms against 436.5 (431; 452) ms ($p<0.001$).

A strong correlation between QTc duration and the presence of hypoglycemia was determined ($r_s=0.78$;

$p=0.023$). QTc duration also correlated with GR ($r_s=0.23$; $p=0.016$) and SD ($r_s=0.21$; $p=0.021$).

Our study involved patients with type 2 DM under the age of 65 years without severe diabetic complications and other factors that, according to the literature, contribute to the extension of the QTc interval [5].

Table 4

Daily characteristics of QTc interval in patients with diabetes mellitus type 2 depending on presence/absence of hypoglycemia (median and interquartile range Me) (25 %;75 %)

Values	Group 1 (n=31)		Group 2 (n=37)	
	without hypoglycemia	with hypoglycemia	without hypoglycemia	with hypoglycemia
QTc daily (ms)	421 (415; 436)	445 (439; 472)*#	425 (417; 439)	448 (431; 496)*#
QTc > 450 (%)	9 (5; 13)	24 (12; 29)*#	9.5 (6; 13)	28 (14; 36)*#

Notes: 1. * – $p<0,05$ compared to structure of control; 2. # – $p<0,05$ compared to patients without hypoglycemia of the corresponding group.

According to our results disruption of myocardial repolarization was determined in patients with type 2 DM, in whom hypoglycemic episodes were recorded during CGM and the level of HbA1c and Gmax did not have a significant effect on the duration of the QTc

interval. The same results were obtained in numerous studies during both spontaneous and induced hypoglycemia in patients with type 1 and type 2 DM [14].

The causes and mechanisms of sudden death in patients with DM have been studied for the past 30 years.



Data on this phenomenon were first published in 1991 by Tattersall R.B. and Gill G.V., who described 22 cases of unexplained sudden deaths in patients with type 1 DM during sleep at night and the absence of any specific morphological signs on autopsy in the United Kingdom performed in the year 1989. 14 of the 22 deaths had a history of grave hypoglycemic conditions [13]. This phenomenon is called "dead in bed syndrome". The pathogenesis of sudden death due to hypoglycemia remains uncertain, which is partly due to the infrequency of this phenomenon, despite the high incidence of hypoglycemia in patients with type 1 DM. The main proposed hypotheses of this pathological mechanism include disorders of autonomic regulation due to severe recurrent hypoglycemia. These conditions have a proarrhythmogenic effect caused by disruption of myocardial repolarization, a marker of which is a prolonged QT interval [3].

Quite insignificant prevalence of this phenomenon in comparison with the frequency of hypoglycemia suggests a possible genetically determined predisposition to changes in the functioning of ion channels. For a long time it was not possible to confirm the connection between hypoglycemia and the development of sudden death, but in 2010 Robert J. Tanenberg and co-authors described the death of a 23-year-old patient with type 1 DM on the background of glycemia 30 mg/dL recorded during CGM [12].

Kacheva S. and co-authors found a decrease in extracellular potassium and an increase in adrenaline as a result of a constrictor response to hypoglycemia in a hypoglycemic clamp test. Therefore, it is believed that the extension of the QT interval occurs due to disruption of potassium ion channels caused by the activation of Na/K-ATPase and changes in myocardial response to catecholamines. Adrenaline in turn acts directly on cardiomyocytes, or indirectly through β -adrenoceptors and causes a delay in the inactivation of incoming calcium flows, which also leads to the extension of the action potential. Interestingly, in laboratory-induced hypoglycemia, the prolonged QT interval was reduced by the introduction of β -blockers, which is consistent with the hypothesis of impaired autonomic support of cardiac activity with a predominance of hypersympathicotonia during a hypoglycemic episode [11].

Although in the analysis of the literature we did not find a description of "dead in bed syndrome" in patients with type 2 DM but our results indicate the similarity of pathogenetic mechanisms of prolongation of the QT interval in patients with type 1 and type 2 DM. Jensen M.H. and co-authors analyzed mortality among patients with type 1 and type 2 DM with severe hypoglycemia in Denmark between

1996 and 2017. This study showed that in a cohort of patients with diabetes with severe hypoglycemic conditions, mortality was significantly higher: 1.11 times – in patients with type 1 DM and 1.77 times – in patients with type 2 DM [4]. In addition, the association between hypoglycemia and increased mortality in patients with type 2 DM was proven in the ACCORD study, by the results of which the intensification of antihyperglycemic therapy significantly increased mortality by 22% [9].

The invention of CGM systems has allowed a broader approach to the assessment of glycemic control in patients with DM. The advantage of this method of estimating DM compensation is the ability to determine the time of glycemia in the target range, the frequency of hypoglycemia and the GV over time. To date, the negative role of high GV in the development of diabetic macro- and microvascular complications has been proven [8]. In addition, according to a meta-analysis conducted by Liang et al. it has been determined that the decrease in GV is associated with a decrease in insulin resistance, a decrease in the thickness of the intima-media and a decrease in cardiovascular risk [7]. It is proven that high GV is a prognostic factor for the development of hypoglycemia and increases the risk of severe hypoglycemia, as well as death from all causes [8].

The data from our study on the relationship between GV and QTc interval duration in patients with type 2 DM coincide with the results of Sertbas Y. and co-authors, who emphasize the importance of determining GV as an additional criterion for assessing glycemic control [15].

CONCLUSIONS

1. In patients with type 2 diabetes mellitus, hypoglycemia has the most significant effect on the duration of the QTc interval, while the level of glycosylated hemoglobin and maximal glycemia do not significantly affect the process of myocardial repolarization.
2. Regardless of the state of glycemic control in our examined patients with type 2 diabetes mellitus, it was determined that the increase in glucose variability is associated with prolongation of the QTc interval.
3. Avoidance of hypoglycemic states is the main goal of preventing QTc prolongation in patients with type 2 diabetes mellitus.
4. Assessment of glucose variability should be mandatory in patients with type 2 diabetes mellitus in addition to traditional glycemic control indicators such as glycosylated hemoglobin, fasting and postprandial glycemia.

Contributors:

Pertseva N.O. – conceptualization, methodology, supervision, validation, writing – review & editing;

Moshenets K.I. – formal analysis, investigation, resources, data curation, writing – original draft.

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