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Вариабельность гликемии при сахарном диабете: инструмент для оценки качества гликемического контроля и риска осложнений

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Стандартный подход к оценке эффективности лечения сахарного диабета (СД) по уровню гликированного гемоглобина (HbA_{1c}) предполагает контроль среднего уровня гликемии, но не учитывает размаха и частоты ее колебаний. Разработка методов математического анализа осцилляций гликемии привела к созданию концепции вариабельности гликемии (ВГ) при СД. Интерес к изучению ВГ резко возрос с появлением технологий непрерывного мониторирования уровня глюкозы, давших возможность подробного изучения временной структуры гликемических кривых. В последние 5 десятилетий предложено множество различных методов оценки ВГ, характеризующих колебания гликемии в разных диапазонах значений, в разные временные отрезки, а также определяющих риск гипо- и гипергликемии. Накапливаются данные о значении ВГ как значимого предиктора диабетических осложнений СД. В ряде проспективных исследований установлено, что параметры ВГ имеют самостоятельное значение в прогнозировании диабетической ретинопатии, нефропатии и сердечно-сосудистых осложнений. Имеются данные о связи ВГ с выраженностью атеросклеротического поражения сосудов и исходом кардиоваскулярных заболеваний у пациентов с СД. Механизмы, лежащие в основе взаимосвязи между ВГ и сосудистыми осложнениями, интенсивно изучаются. Недавние исследования показали, что эффект ВГ на сосудистую стенку может реализоваться через окислительный стресс, хроническое воспаление, дисфункцию эндотелия. Средний уровень гликемии и ВГ являются самостоятельными предикторами гипогликемий у больных СД. Кроме того, повышенная ВГ ассоциирована с нарушением гормонального ответа на гипогликемию и может являться предиктором нарушенного распознавания гипогликемий в долгосрочной перспективе. Представленные данные дают основание считать, что применение математических методов анализа ВГ у пациентов с СД является перспективным инструментом для индивидуализированной оценки гликемического контроля, риска сосудистых осложнений и гипогликемий. Вероятно, уменьшение ВГ можно рассматривать как одну из терапевтических целей при лечении СД.
Ключевые слова: *сахарный диабет; вариабельность гликемии; непрерывный мониторинг гликемии; гипогликемия; сосудистые осложнения; факторы риска*

Glycaemic variability in diabetes: a tool for assessing the quality of glycaemic control and the risk of complications

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The routine approach to evaluating the effectiveness of diabetes treatment based on the level of glycated haemoglobin (HbA_{1c}) accounts for the average glucose level but does not consider the scope and frequency of its fluctuations. The development of computational methods to analyse glycaemic oscillations has made it possible to propose the concept of glycaemic variability (GV). The interest in research focused on GV increased dramatically after continuous glucose monitoring (CGM) technology was introduced, which provided the opportunity to study in detail the temporal structure of blood glucose curves. Numerous methods for assessing GV proposed over the past five decades characterize glycaemic fluctuations as functions of concentration and time and estimate the risks of hypoglycaemia and hyperglycaemia. Accumulating evidence indicates that GV may serve as a significant predictor of diabetic complications. Prospective studies demonstrate that certain GV parameters have independent significance for predicting diabetic retinopathy, nephropathy and cardiovascular diseases. There is evidence that GV correlates with the severity of atherosclerotic vascular lesions and cardiovascular outcomes in diabetic patients. The mechanisms underlying the relationship between GV and vascular complications are being intensively studied, and recent data show that the effect of GV on vascular walls may be mediated by oxidative stress, chronic inflammation and endothelial dysfunction. Average blood glucose levels and GV are considered independent predictors of hypoglycaemia. Increased GV is associated with impaired hormonal response to hypoglycaemia and is a long-term predictor of hypoglycaemia unawareness. These data allow us to conclude that computational methods for analysing GV in patients with diabetes may serve as a promising tool for personalized assessment of glycaemic control and the risk of vascular complications and hypoglycaemia. Thus, the reduction of GV can be regarded as one of the therapeutic targets to treat diabetes.
Keywords: *diabetes; glycaemic variability; continuous glucose monitoring; hypoglycaemia; cardiovascular complications; risk factors*

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Improvement of the methods for assessing the quality of glycaemic control and predicting cardiovascular complications in patients with diabetes mellitus (DM) is one of the most relevant tasks of diabetology. The routine approach to evaluating the effectiveness of diabetes treatment based on the level of glycated haemoglobin (HbA_{1c}) accounts the average blood glucose level but does not consider its fluctuations. Meantime, new data support the importance of glycaemic variability (GV) as an independent predictor of diabetes complications. The interest in research focused on GV increased dramatically after introduction of methods for continuous glucose monitoring (CGM), which provided an opportunity to investigate the temporal structure of blood glucose curves. In this review, we summarize data regarding the methods for assessing and clinical significance of GV in patients with diabetes.

METHODS FOR ASSESSING GLYCAEMIC VARIABILITY

About 30 different criteria characterizing GV have been introduced since the 1960s. The results of blood glucose self-monitoring or CGM are used to determine these criteria. We will consider the main parameters used to assess GV.

Standard deviation (SD) is a frequently used conventional GV parameter characterizing the degree of dispersion of blood glucose levels. The coefficient of variation (CV), which indicates the percentage of SD from the mean blood glucose level, is the derivative criterion. Another commonly used parameter is the mean amplitude of glycaemic excursions (MAGE). All fluctuations with amplitudes <1 SD are excluded from MAGE calculation. MAGE is commonly used to analyse CGM data, while SD and CV are applied to analyse the results of self-monitoring [1]. The advantages of these methods for assessing GV include simple calculations and the absence of specific requirements for the frequency and duration of glycaemic control. A disadvantage is its limited informative value because these parameters do not account the frequency of blood glucose fluctuations and range (hypo-, hyper- or euglycaemia).

The area under the curve (AUC) is another commonly used parameter of GV and is the most informative for assessing the short-term changes in blood glucose, for example, increased glucose level after a meal [2, 3] or standard glucose load [4, 5]. Software for CGM devices typically calculates AUC automatically.

The *continuous overlapping net glycaemic action (CONGA)* parameter was specifically designed to analyse CGM data by estimating the intraday variability of glucose levels. The absolute difference in blood glucose values at a given point and n hours earlier is determined to calculate this parameter. Differences in blood glucose levels are calculated after n hours of monitoring. The CONGA index shows the variance (standard deviation) of the differences [6].

The common disadvantage of conventional GV indicators is their insufficient sensitivity to hypoglycaemia. New criteria for evaluating GV were developed to overcome this limitation. The lability index (LI) is specifically designed to assess the risk of severe hypoglycaemia and represents the difference between blood glucose values for three consecutive points (i.e. two consecutive intervals). The results for the required time are added and then divided by the number of hours. When used together with the specially designed hypoglycemic score (HYPO score), which accounts the frequency and severity of hypoglycaemia episodes and hypoglycaemia unawareness, this method allows one to identify patients who are candidates for islet transplantation according to their long-term risk of severe hypoglycaemia [7].

Nevertheless, the methods described above are not effective enough for timely prediction of hypoglycaemia for a individual patient. The reason for this is that the blood glucose measurement scale is asymmetric because the magnitude of fluctuations in the hyperglycaemic range is higher than that in the hypoglycaemic range. Therefore, MAGE values and several other parameters correlate more closely with the frequency of hyperglycaemia than hypoglycaemia [8]. Kovatchev et al. proposed a solution to the problem caused by scale asymmetry as follows: they suggested using a mathematical transformation (logarithmation), which generates a symmetric midrange blood glucose scale (3.9–10.0 mmol/l) [9]. Further, they proposed assigning a risk value to each blood glucose level as follows: 6.0 mmol/l corresponds to risk 0, and the risk increases when approaching hypoglycaemic values, leading to the introduction of the *low blood glucose index (LBGI)*.

The LBGI detects hypoglycaemia with high sensitivity and predicts 57% of cases of severe hypoglycaemia [9]. The *high blood glucose index (HBGI)* was subsequently introduced [10], and the *average daily risk range (ADRR)* was proposed. The ADRR sums the risks of hypoglycaemia and hyperglycaemia; therefore, it is highly sensitive to both conditions. It is important that when calculating ADRR, the reference blood glucose values are assigned a smaller 'weight coefficient' of risk; therefore, fluctuations within the reference range are less significant than beyond it, and increasing risk values are assigned to the fluctuations towards extreme hypoglycaemia or hyperglycaemia [8]. ADRR was successfully applied to analyse CGM data. This parameter remains one of the best for assessing the quality of blood glucose control because of its high sensitivity and prognostic value [11–13]. Moreover, ADRR selects patients with different risks of glycaemic lability [14].

Assignment of the risk level to each range of the blood glucose scale is used in other methods for evaluating GV. Thus, the *glycaemic risk assessment diabetes equation (GRADE)* uses the scale produced by assigning a risk level to each of 40 different glucose concentrations. The GRADE scale allows one to determine the risk of hypoglycaemia and hyperglycaemia based on a particular patient's glycaemic profile [15]. Note that GRADE, ADRR, HBGI and LBGI should be regarded as indicators of the quality of glycaemic control rather than the actual GV parameters.

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Table 1

Reference values (M + 2 SD) of GV parameters in patients without DM (according to [11] in the abridged form)

Parameter	LLN	ULN
SD, mmol/l	0,0	3,0
CONGA, mmol/l	3,6	5,5
LI. (mmol/l)^2/h	0,0	4,7
J-Index, (mmol/l)^2	4,7	23,6
LBGI	0,0	6,9
HBGI	0,0	7,7
GRADE	0,0	4,6
MODD, mmol/l	0,0	3,5
MAGE (variant for CGM), mmol/l	0,0	2,8
ADRR	0,0	8,7

The mean of daily differences (MODD) was proposed to assess interday glycaemic variations [16] and represents the average difference between blood glucose levels obtained at the same time on two consecutive days. The MODD parameter is used to analyse blood glucose self-monitoring or CGM data [1]. Evaluation of longer-term GV (e.g. changes in HbA_{1c} level) was also suggested [17, 18].

The limits of reference ranges were determined for the most common GV parameters (Table 1). The reference values were obtained when analysing the results of the 72 h CGM in 78 healthy people [11]. A recent study shows that GV increment of with increased insulin resistance and dysfunction of β-cells in patients with impaired glucose tolerance, impaired fasting glucose and in patients with type 2 diabetes [19]. The mean blood glucose levels, SD, HGBI, CONGA, MODD and MAGE significantly increase as normal carbohydrate metabolism progresses to diabetes [19].

Thus, methods are available for assessing GV, which allow quantitative estimation of glycaemic fluctuations in different ranges and at different times. GV parameters can be used to individualise assessment of the glycaemic profile in patients with diabetes.

PROGNOSTIC VALUE OF GLYCAEMIC VARIABILITY

The risk of vascular complications

Analyses were conducted on data accumulated since the late 1990s on the association between GV and the development of diabetes. For example, analysis of the data reported by the Diabetes Control and Complication Trial (DCCT) showed a relationship between long-term GV determined according to the changes in HbA_{1c} level as a function of the risk of microvascular complications. HbA_{1c} variability was determined for 1441 patients with type 1 diabetes, and the progression of complications was evaluated for 9 years. A 1% increase in SD of the HbA_{1c} level correlated with increased risks of retinopathy (HR = 2.26, p < 0.0001) and nephropathy (HR = 1.8, p <0.0001). The average HbA_{1c} level also predicted these complications [17]. The risk of diabetic microvascular complications was not affected by GV values (AUC and SD) calculated according to the quarterly levels of pre- and postprandial glucose in 7 points. Thus, the contribution of short-term GV in the development of microangiopathy in patients included in DCCT has not been proven [20]. An analysis of the results of the follow-up phase (the EDIC project) showed that the risks of developing retinopathy and nephropathy by the fourth year after completion of the DCCT depended on the average blood glucose and HbA_{1c} levels during the study. No long-term effect of GV parameters on the development of microvascular complications was detected [21].

In the prospective, observational FinnDiane study (Finnish Diabetic Nephropathy Study), which included 2,107 patients with type 1 diabetes, the variability (SD) of HbA_{1c} was associated with the risk of progression of diabetic nephropathy (HR = 1.92, p <0,001) and cardiovascular complications (HR = 1.98, p <0.001). This association remained significant after accounting for the average HbA_{1c} level and conventional risk factors. The average HbA_{1c} level was not a predictor of progression of complications during 5.7 years of follow-up [18]. In has been shown that, patients with the highest HbA_{1c} variability (within the upper quartile) were at higher risk of developing proliferative retinopathy (HR = 1.7, p <0.01) and higher probability of retinal laser photocoagulation (HR = 1.6, p = 0.02) compared with patients with HbA_{1c} variability within the lower quartile [22].

In the prospective observational Verona Diabetes Study, which included 1,409 patients with type 2 diabetes, CV was an independent predictor of death caused by diabetes, cardiovascular complications and cancer during 10 years of monitoring [23]. In patients of advanced age, cardiovascular mortality was associated with variability (but not the level) of fasting blood glucose. High GV values (within the upper third of the range) increased the risk of death caused by cardiovascular diseases by 2.4 times [24].

Evidence of an association of GV with atherosclerosis, coronary artery disease and its complications were provided by several small-scale studies. In patients with type 2 diabetes, a direct correlation was established between GV parameters calculated based on the CGM data and carotid intima-media thickness [25, 26]. MAGE was an independent predictor of the degree of coronary atherosclerosis, along with age, the level of C-reactive protein and HbA_{1c} in patients with type 2 diabetes and with angiographically verified coronary heart disease [27]. Further, the high amplitude of diurnal fluctuations of blood glucose levels (MAGE > 5 mmol/l) increased the risk of high-grade ventricular arrhythmias by a factor of 2.3 in patients with type 2 diabetes [28]. In erderly patients MAGE calculated based on CGM parameters was a more powerful predictor of the risk of cardiovascular events (myocardial infarction, congestive heart failure, death) than HbA_{1c} within the first year after myocardial infarction [29, 30]. In diabetic patients who underwent coronary artery bypass surgery, high GV was associated with a high risk of postoperative complications [31].

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The mechanisms of action of glycaemic fluctuations on the vascular wall have not been fully elucidated. It was demonstrated in vitro that transient hyperglycaemia increase the production of free radicals in human endothelial cells and enhances apoptosis [32]. However, no association between CGM-defined GV parameters (MODD, MAGE, CONGA) and urinary excretion of the oxidative stress marker 15(S)-8-iso-prostaglandin was established in patients with type 1 diabetes [33]. Nevertheless, modelling of glycaemic fluctuations in healthy volunteers and in patients with type 2 diabetes under hyperinsulinaemic-euglycaemic clamp conditions shows that periodic fluctuations of glucose concentration from 5 to 15 mmol/l activated free radical processes and reduced the flow-dependent vasodilation to a greater extent than stable hyperglycaemia at the level of 10 or 15 mmol/l [34]. Repeated hyperglycaemic peaks in diabetic animals increases monocyte adhesion to vascular endothelium to a greater extent than does stable hyperglycaemia [35]. Hyperglycaemic peaks may have a long-term effect on endothelial cells via epigenetic modifications of gene regulatory regions. Further, transient hyperglycaemia induces epigenetic modification in the promoter of the gene encoding nuclear factor NF-kB p65 subunit in aortic endothelial cells, with subsequent activation of NF-kB p65 and enhancement of the expression of inflammatory mediators (MCP-1 and VCAM-1) controlled by this gene. The effects of increased glucose levels are mediated via increased production of free radicals and continue to persist for six days under normoglycaemic conditions [36]. The hyperglycaemic peaks may induce long-term self-sustaining processes in vessels, such as oxidative stress and chronic inflammation, which play an important role in 'metabolic memory' and in development of diabetic angiopathy [37, 38].

HbA_{1c} is well-known predictor for cardiovascular complications of diabetes. Several studies examined the relationship between the HbA_{1c} level and GV parameters. Comparison of the HbA_{1c} level with the average level and SD of blood glucose in patients with type 1 and type 2 diabetes acquired by self-monitoring for three months, shows that the HbA_{1c} level affects the average blood glucose level but not its variability [39]. In patients with type 2 diabetes with good glycaemic control ($HbA_{1c} < 7\%$), the HbA_{1c} level does not correlate with GV parameters (SD graduation, MAGE) calculated based on CGM [40].

Thus, the HbA_{1c} level and GV are complementary characteristics of glycaemic control. The significance of GV in prediction models of cardiovascular complications should be analysed allowing for the predictive effect of HbA_{1c}. However, how GV influences the risk of development of micro- and macrovascular complications of diabetes remains unanswered because the relatively small number of studies report contradictory results. The discrepancies are due to differences in clinical and experimental models and different approaches to GV analysis. Identification of the role of GV in the development of diabetic angiopathy is a promising direction for further research.

Hypoglycaemia risk

An analysis of the DCCT data shows that the HbA_{1c} level, the average blood glucose level and GV (SD) are independent and complementary predictors of hypoglycaemia in patients with type 1 diabetes. Increased GV is associated with the risk of repeated episodes of hypoglycaemia. Accounting for the effect of HbA_{1c}, an increase in SD of blood glucose by 1 mmol/l increases the risk of the first and fifth hypoglycaemic episodes by factors of 1.09 and 1.12, respectively [41]. Higher values and variability of HbA_{1c} are associated with the risk of hypoglycaemia in diabetic patients receiving haemodialysis [42]. According to our data, SD of blood glucose values recorded during the two-day CGM predicts hypoglycaemic episodes elderly type 2 diabetic patients treated with insulin [43].

There is evidence that increased GV in patients with DM is associated with impaired physiological response to hypoglycaemia and impaired recognition of hypoglycaemia. For example, simulation of hypoglycaemia under hyperinsulinaemic clamp demonstrate that GV parameters (ADRR and LBGI) in patients with type 1 diabetes, determined based on the results of one-month blood glucose self-monitoring, correlated negatively with the severity of the adrenal response to hypoglycaemia [13]. The response of the adrenal glands and the autonomic nervous system to hypoglycaemia may be reduced in patients with any type of diabetes. This leads to repeated episodes of hypoglycaemia and generation of a vicious cycle, which dramatically increases GV.

Even a single hypoglycaemic episode in patients with type 1 diabetes in the evening impairs the adrenal response and severity of symptoms of hypoglycaemia the next morning [44]. Similarly, in patients with type 2 diabetes, an episode of hypoglycaemia during the previous day delays the release of glucagon and catecholamines and reduces the severity of adrenergic and neuroglycopenic symptoms during hypoglycaemia on the next day. The recent hypoglycaemia contributes to impairment of a counter-regulatory response and hypoglycaemia unawareness. It was established that increased insulin sensitivity, increased risk of hypoglycaemia and decreased adrenal response to hypoglycaemia measured using biochemical methods are associated with increased GV (ADRR, LI, LBGI) regardless of HbA_{1c} level [45].

These findings explain why the episodes of severe hypoglycaemia in patients with type 1 diabetes often occur during periods of increased GV, which can be observed retrospectively according to self-monitoring data. Kovatchev et al. demonstrated such 48-hour periods before and after severe hypoglycaemia [9]. Calculation of the SD of blood glucose levels acquired by one-month self-monitoring in patients with type 1 diabetes (100 measurements) allows one to predict the development of impaired recognition of hypoglycaemia within 11 years after disease onset [46]. These data, taken together, support the conclusion that the use of GV analytical methods in diabetic patients is a valuable tool to determine individual risk of developing hypoglycaemia.

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CONCLUSIONS

Assessment of GV is a promising approach to evaluate the effectiveness of diabetes control. The data accumulated to date suggest that the use of GV parameters, together with HbA_{1c} level and other conventional risk factors, can improve the accuracy of predicting cardiovascular complications and hypoglycaemia. The reduction of GV may be regarded as one of the targets for treating diabetes. According to the preliminary data, insulin analogues [47], insulin pumps [48], incretins and incretin mimetics [49, 50] and real-time CGM [51] make it possible to reduce GV. Further research should focus on determining the most informative GV parameters for assessing the quality of glycaemic control and the risk of complications in various clinical situations. The mechanisms of the effects of glycaemic fluctuations on the development of diabetes complications and outcomes require further investigation. The effect of different modes of antihyperglycaemic therapy on GV should be estimated in randomized clinical trials.

DISCLOSURE INFORMATION

The authors declare that there is no conflict of interest.

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