Abstract. Cardiac autonomic neuropathy (CAN) is closely associated with an approximately five-fold increase in the risk of cardiovascular mortality in patients with diabetes mellitus (DM). Impaired autonomic function of the cardiovascular system in DM, which leads to the development of CAN, can be accompanied by coronary artery ischemia, heart rhythm disturbances, “silent” myocardial infarction, severe orthostatic hypotension, and sudden cardiac death syndrome. The article provides an analysis of literature data on the impact of glycemic variability (GV) on diabetic CAN development. This review analyzed the possible relationships between GV in people with diabetic CAN. In particular, the issues related to glycemic control and CAN, the link between GV and CAN in diabetes were analyzed. Unsatisfactory glycemic control and uncontrolled glycemic status are considered the main risk factors for chronic complications of DM, in particular CAN. An increase of GV is associated with a higher risk of chronic complications of DM, cardiovascular risk, all-cause mortality and morbidity. The clinical trial results demonstrated that time in range might be a promising metric for assessing glycemic control and prognosis of diabetic complications. This review is based on a search in PubMed and MEDLINE, Scopus, BIOSIS, EMBASE, Google Scholar and Springer Online Archives Collection. The following keywords were used: glycemic variability, cardiac autonomic neuropathy and diabetes mellitus. Research findings missed by the web search have been identified through a manual search of the bibliography of publications. CAN is one of the frequent long-term complications of DM, and reasonable control of GV may be necessary for its prevention. Determination of GV may have advantages for predicting future complications of DM in clinical trials and practice. The association of autonomic dysfunction and glucose levels, insulin resistance, and HbA1c variability suggest further research to reduce chronic complications development. Further investigation is needed to study the mechanisms of GV and evaluate them as therapeutic targets in the treatment of patients with T2DM.

Keywords: diabetes mellitus; cardiac autonomic neuropathy; glycemic variability

Introduction

Maintenance of homeostasis, adequate responses to stress, and features of spatial compartmentalization belong to the biological causes or hallmarks of health. Disturbance in at least one of these interlocked aspects is commonly pathogenic, causing a progressive or acute derailment of the system and the loss of numerous stigmata of health [1]. Circadian rhythm is one of the main regulators of physiological parameters [1, 2].

Circadian hormones synthesis, autonomic nervous system (ANS) regulation, and changes in heart rate (HR) and blood pressure (BP) parameters lead to variations in cardiovascular diseases (CVD) incidence within the 24-h period [3, 4]. Thus, investigations of the circadian rhythm, especially a link between cardiovascular rhythmicity and CVD development are of special interest [5]. Variability, in the broadest sense of the term, is of fundamental importance in all major control systems in the body. It is known that insulin action and glucose tolerance are connected with the circadian rhythm of hormones synthesis [6, 7]. A certain degree of glycemic variability (GV) is observed during physiological glucose tolerance [8]. However, GV increases in the state of diabetes mellitus (DM) and impaired blood glucose regulation [9, 10].
A significant consequence of DM known as cardiac autonomic neuropathy (CAN) is closely linked to around five-fold higher risk of cardiovascular mortality [11, 12]. According to the Toronto Consensus Panel on Diabetic Neuropathy, CAN is defined as “impaired cardiovascular autonomic function in terms of DM after excluding other causes” [13]. The ANS damage that leads to the development of CAN may be accompanied by coronary artery ischemia, heart rhythm disorders, “silent” myocardial infarction, severe orthostatic hypotension, and sudden cardiac death syndrome [14–16].

In this review, we analyzed the literature on the possible relationships between glycemic control and CAN, the relationship between GV and CAN in DM.

Search strategy. This review is based on a search of PubMed and MEDLINE, Scopus, BIOSIS, EMBASE, Google Scholar and Springer Online Archives Collection were used to conduct a search of the literature. The following keywords were used: glycemic variability, cardiac autonomic neuropathy, and diabetes mellitus. Research findings missed by the web search have been identified through a manual search of the bibliography of publications.

Cardiac autonomic neuropathy and diabetes mellitus

In persons with type 1 DM (T1DM) and type 2 DM (T2DM), the prevalence of CAN varies from 1 to 90 and 20 to 73 %, respectively [17]. Research by A. Moștădianu et al. (2018) demonstrated that CAN is a more common complication of T1DM [18]. However, due to inconsistent diagnostic criteria and notable population differences, particularly in terms of CAN risk variables (such as age, gender, and DM duration among others), there is a broad variation in the prevalence of CAN [19, 20].

According to data obtained from cross-sectional or longitudinal studies, clinical predictors or correlates of CAN were age, glycemic control, diabetes duration, and the presence of other chronic complications of DM [16, 18, 21, 22]. A significant risk factor for CAN development is poor glycemic management [23, 24]. The correlation between glycemic control and CAN in T2DM patients were analyzed in research by C. Achmad et al. (2023) [25].

Therefore, early diagnosis of CAN is an extremely urgent problem of modern diabetology. D. Ewing et al. (1980) [26] suggested five tests to assess autonomic function. The Toronto Diabetic Neuropathy Expert Group states that the time-domain HR response to deep breathing, theValsalva maneuver, and postural change are the most commonly used tests for determining cardiac parasympathetic activity. The test with the highest specificity (80 %) is HR to deep breathing. Cardiovascular sympathetic function is evaluated by assessing Valsalva maneuver and the BP response to orthostatic change [20, 27]. The frequency domain analysis of the short-term ECG recordings is possible with specialized software. A second approach to CAN diagnosis can be based on heart rate variability (HRV) evaluation during 24-h Holter ECG monitoring and the application of statistical indicators in the time and frequency domain [28, 29]. CAN can also be detected using positron emission tomography with analogs of sympathetic neurotransmitters, single-photon emission computed tomography; the baroreceptor reflex, and heart rate turbulence [30].

Glycemic variability

Glycemic variability is established as glycemic excursions throughout the day, including low and high glucose levels [31, 32]. The evaluation of GV can be performed in different ways, namely long-term, intermediate-term and short-term. There is a need for future investigations of the possible differences between mean HbA1c and long-term GV in the contribution to the prognosis of a patient with DM [33, 34].

Glycemic variability can be evaluated using a wide range of various techniques. Although numerous indicators have been suggested, there still needs to be a defined gold-standard technique for assessing GV in clinical practice [35]. The following continuous glucose monitoring (CGM) indicators are specifically determined: low blood glucose index (LBGI), high blood glucose index (HBGI), average daily risk range, mean amplitude of glucose excursion (MAGE), mean of daily differences (MODD), continuous overall net glycemic action (CONGA), mean (average) standard deviation (SD), J index, coefficient of variation (CV) [36].

Many of these indices can now be accessed by downloading self-monitoring blood glucose (SMBG) data, making them accessible to patients and physicians. Other indices are quite difficult even when calculated using blood glucose monitoring technologies like CGM. Most research that looked at the correlation between various assessment methods showed that the most popular ones are tightly connected and with previously created measures used to measure HbA1c variability [9, 36].

Diabetes Control and Complications Trial (DCCT) showed the primary role of GV in microvascular complications development, namely intensive therapy reduces the manifestation of diabetic retinopathy (DR) and its further progression, as well as other T1DM complications. Identical results apply to other microvascular complications, namely nephropathic and neuropathic outcomes. The investigators concluded that only 11 % of the variation in the risk of DR could be due to higher HbA1c levels, so other factors are responsible for the remaining 89 % [9]. The negative impact of GV in developing diabetic micro- and macrovascular complications is proved in clinical trials [37]. It has been suggested that an unsatisfactory state of GV may have a more harmful effect than chronic hyperglycemia on the development of cardiac autonomic dysfunction in T2DM [38–40].

According to the International Consensus, the primary measurable outcomes of CGM are the mean glucose, time in range (TIR), glucose management indicator (GMI), GV, time above range (TAR) and time below range (TBR). For the interpretation of obtained data from CGM it should be at least 10 days of valid data from more than 14 days of recording [41]. For patients using CGM TIR was defined as the time in the target range of glycemia between 70 and 180 mg/dL with reducing TBR [42]. Additionally, numerous parameters of CGM can be used for GV assessment, namely SD, CV, MAGE, mean absolute glucose (MAG), MODD, J index, CONGA, LBGI, HBGI, an area under the curve hypoglycemia [43].

The development of chronic complications of DM is explained by the negative impact of glycemic peaks and nadirs (dysglycemia) as well as by chronic hyperglycemia. Chronic vascular complications development is caused by several pathophysiological mechanisms, which combine oxidative
Glucose variability and diabetic cardiac autonomic neuropathy

At the pre-diabetes stage, there is an increase in glucose level variability, which can be used as an additional parameter to assess glucose homeostasis [49]. The research results by I. Hirsch et al. (2019) [50] indicate that the treatment’s main goal should be controlling GV, as the sharp fluctuations in the blood glucose level are harmful. Therefore, future investigations are needed on the pathophysiological contribution of GV to increased cardiovascular risk and the development of autonomic cardiac dysfunction [51].

Currently, it is not known for certain whether GV is associated with CAN. Only in a few trials the impact of GV on the stage of CAN in persons with T2DM was studied [52]. J. Jun et al. (2015) investigated the impact of GV on CAN development. This study included 110 persons with T2DM who underwent a three-day CGM. Univariate analysis demonstrated the increase in all parameters of HbA1c variability among CAN (+) persons. Multivariate analysis demonstrated the independent correlation of coefficient of variation of HbA1c (HbA1c-CV) with CAN, but no dependence for SD and MAGE was found. A significant association of SD of HbA1c (HbA1c-SD), log CV of HbA1c and adjusted SD of HbA1c with the CAN was found. An increased risk of CAN progression was seen in individuals with higher HbA1c-CV [53]. Thus, CGM results indicate that the development of CAN in individuals with poor control of T2DM is independently associated with CV and all variability parameters.

The correlation between glycemic control and CAN in T2DM patients were analyzed in research by C. Achmad et al. [25]. Multivariate analysis showed that mean HbA1c was significantly correlated with cardiovascular autonomic tests score even after adjustment for DM duration and treatment, age and gender [25]. However, it has been reported that improvement in glycemia alone does not indicate an improvement in cardiac autonomic function in T2DM. In particular, the Veterans Affairs Cooperative Study on T2DM was to analyze the effect of 24 months of intensive hypoglycemic therapy on the prevalence of peripheral or autonomic neuropathy. Obtained results demonstrated that 2 years of intensive therapy was accompanied by a slight improvement in neuropathy and apparent improvement in upper extremity touch sensation and cranial neuropathy [54].

A study of the relationship between GV and CAN was performed by W. Xu et al. (2016) included 90 patients with newly diagnosed T2DM who underwent CGM lasting from 48 to 72 hours, and the CV of glycemia, MAGE, and MODD were calculated. Obtained results demonstrated that 22.2 % of persons were diagnosed with CAN. In the CAN (+) group was found an increase in MAGE and a tendency to increase in GV. A significant relationship between MAGE and CAN was established by logistic regression analysis. The researchers concluded that MAGE is a significant predictor of CAN and GV is related to CAN development in newly diagnosed T2DM [55].

The possible relationship between ANS and GV in T2DM persons was investigated by S. Kalopita et al. (2014). After adjusting for HbA1c and disease duration, the inverse association between HRV and the standard deviation of mean glucose level was found. Most HRV indicators in the time domain were significantly correlated with the SDMG, but a stronger association for nocturnal HRV parameters was found. The authors concluded that in patients with T2DM, HRV is inversely associated with GV, which proves the connection between autonomic dysfunction and GV [56]. The research results on T2DM confirm that short-term GV is involved in microvascular complications pathogenesis [57]. It has been proven that there is bidirectional regulation between glucose metabolism and ANS activity [58].

The results of several studies indicate that one of the key risk factors for CAN development is GV. In particular, it was reported that violations in ANS balance, namely fluctuations in sympathetic activity after awakening, were positively correlated with GV in patients with T2DM [59].

Although the factors of CAN progression are known, the reversibility of ANS dysfunction remains open. J. Jun et al. (2019) investigated clinical factors associated with CAN re-
covery. In a retrospective longitudinal study, patients with T2DM and CAN without CVD’s at baseline were observed for 2–3 years. Recovery was classified as partial and complete; for complete, the normalization from definite or severe CAN should be obtained. Among the 759 patients with CAN, 29.9% were found to be recovered from CAN, and 1.2% had fully recovered. Partial and complete recovery from CAN was observed in patients of younger age, with a shorter duration of DM, without the presence of micro/macrolambumiria, and with a reduction of HbA1c and body weight. Among the associated factors, the highest importance belongs to younger age. In a multivariable model, younger age was the only significant factor for complete recovery of CAN [60]. F. Wei et al. (2016) conducted a study which involved 239 T2DM persons. The impact of GV on the progression of renal and endothelial dysfunction was investigated. SD and CV of serially measured fasting plasma glucose and HbA1c were used to calculate visit-to-visit GV. Kidney and endothelial function was assessed at the beginning and at the end of observation. It was demonstrated that an increase in visit-to-visit GV was found to reduce renal and endothelial dysfunction in T2DM persons independently. More sufficient data on the connection between GV and BRS must be provided [61]. D. Matsutani et al. (2018) conducted a multicenter prospective open-label clinical trial to determine the relationship between HbA1c-CV and BRS. The primary objective was to find the possible association between BRS and HbA1c-CV. Univariate analysis revealed an inverse relationship between CGM SD, CGM CV and MAGE with BRS. Additionally, the correlation of BRS with age, estimated glomerular filtration rate, HR, coefficient of variation of R–R intervals, and cardio-ankle index was found. After adjusting BRS for age, gender, dyslipidemia, HR, BP, mean glucose level, cardio-ankle index and estimated glomerular filtration rate, multiple regression analysis demonstrated the significant association of reduced BRS with MAGE and CGM CV. A reduction in BRS after two years of DM duration was also demonstrated independent of gender and age. The study’s results indicate that in patients with T2DM, regardless of the glucose level, GV and HbA1c variability were inversely proportional to BRS independent of mean HbA1c. Considering the obtained results, the authors concluded that HbA1c variability is a marker of BRS reduction in T2DM, and BRS may predict cardiovascular events considering GV [39].

Detailed information on the relationship between CGM-derived GV scores and diabetes complications is presented in a review by M. Yapanis et al. (2022) in the PubMed and Embase databases. The relationship between GV and low TIR with chronic DM complications has been demonstrated. Notably, a higher TIR was associated with DR risk reduction, albuminuria, all-cause mortality, and CVD. An SD of blood glucose and MAGE was connected with peripheral neuropathy. Ergo, the evidence supports the connection between GV indicators and complications of diabetes mellitus [42].

The value of TIR in clinical practice is of growing interest. In a cross-sectional study, R. Dimova et al. (2020) studied the relationship features between some OS markers, heart autonomic function, GV, and indicators of the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in healthy and persons with pre-diabetes. It has been proven that in conditions of pre-diabetes, there is an increase in GV indices and a higher prevalence of cardiac autonomic dysfunction. At the same time, a reliable correlation between OS indicators and the autonomic heart tone was not found. HOMA-IR and TIR were prognostic variables for CAN. The parasympathetic and sympathetic activity were independently associated with J-index in patients with pre-diabetes and negatively correlated with mean glycemic level and GV indices. Thus, the autonomic function of the heart is reduced in pre-diabetes and is probably related to GV and HOMA-IR in the early stages of dysglycemia. In addition, it was suggested that the association of TIR with the development of complications in T2DM and pre-diabetes. The authors believe that exposure to GM can be only an additional risk factor for autonomic dysfunction, which cannot have a more harmful effect than chronic hyperglycemia [51]. At the same time, A. Breyton et al. (2021) rightly observed that the assessment of CGM GV parameters can provide more complete glucose control than standard postprandial monitoring [34]. C. Yang et al. (2020) believe that variability of HbA1c, especially HbA1c CV, may complement traditional baseline HbA1c measures to determine the risk of microvascular complications in T2DM. In persons with T2DM with relatively optimal baseline glycemic control, the significant role in microvascular outcomes belongs to HbA1c variability compared to persons with poor glycemic control [62]. Thus, a key component of dysglycemia in T2DM is GV, and parameters such as TIR, MAGE, and SD can be routinely used alongside traditional measures such as HbA1c, fasting and postprandial plasma glucose [34].

**Time in range**

American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2022 consensus considers TIR as the time in the target range of glycemia between 70 and 180 mg/dL (3.9–10.0 mmol/L) [63]. TIR can be used to assess glycemic control and reduced TIR correlate with a higher risk of microvascular complications [64]. TBR and TAR are also valuable indicators for evaluating treatment regimens. When using an ambulatory glucose profile to assess glycemic control, the target parallel to an HbA1c < 53 mmol/mol (< 7 %) for many is TIR > 70 %, with an additional value of TBR of less than 4 % and time at < 3.0 mmol/L (< 54 mg/dl) less than 1 % [63, 65]. R. Beck et al. (2019) demonstrated that in T1DM, CGM parameters, particularly mean glucose, and TIR, are moderately correlated with HbA1c. I. Hirsh et al. (2019) retrospectively analyzed the results of four randomized trials, including data from 530 adults with T1DM or T2DM treated with insulin. CGM data for more than two weeks and HbA1c parameters were studied. The results suggest that the indicators obtained by CGM are important and help to intensify diabetes therapy independently of HbA1c rapidly [35].

TIR, like HbA1c, has a similar relationship with diabetic microvascular complications [67]. A strong correlation between TIR and HbA1c was reported in the studies of R. Vigersky et al. (2019). This finding allows the transition to TIR as a better indicator for assessing individual patient’s glycemic control, analyzing clinical studies results and predicting chronic complications development. The results of the data
analysis of 3262 patients with T2DM indicate a significant association between TIR and DR after controlling for gender, age, BMI, duration of DM, HbA1c, BP and lipid profile. The association remained significant even after further adjustment for GV metrics [68]. Thus, it was concluded that there is an association between TIR and DR in the state of T2DM [64]. Q. Guo et al. (2020) analyzed the relationship between TIR and CAN among 349 patients with T2DM, including 228 patients with CAN. Obtained results demonstrated that lower TIR was associated with a more severe CAN stage. Simultaneously, the increased TIR was accompanied by a decrease in the severity of CAN. Thus, it was concluded that there is an independent connection between CAN and TIR [69]. Thus, the assessment of CGM, first of all TIR is potentially a perspective outcome measure. Compared with HbA1c testing, TIR provides more sensitive and accurate results. For example, CGM assessment can record acute hypoglycemia or hyperglycemia at any time that cannot be obtained by HbA1c evaluation [68]. It has been established that the GV can assess physiological sources of variation in diabetic complications beyond glycemic control and be a useful clinical research tool [69]. The prospective descriptive study aimed to analyze factors associated with poor glycemic control showed that patients with TIR > 80% have been shown to have better outcomes than patients with TIR < 80%. In addition, frequent hypoglycemic conditions were not recorded in this category of patients [35].

A study of the association of TIR 70–180 mg/dL (3.9–10 mmol/L) with the development or progression of microalbuminuria and DR was conducted by R. Beck et al. (2019). The results indicated an association between a higher risk of microvascular complications and TIR and concluded that TIR should be considered an acceptable endpoint for clinical trials [66].

Conclusions
Continuous glucose monitoring undoubtedly plays a significant role in assessing the safety and effectiveness of T1DM treatment. Only limited evidence suggests that GV is also beneficial in patients with T2DM, particularly those requiring insulin therapy [70–73]. The 2022 ADA/EASD consensus states that routine glucose monitoring has limited additional clinical benefits for people with T2DM not using insulin but also adding burden and cost [72]. However, for some individuals, glucose monitoring, especially in combination with education, can provide insight into the impact of lifestyle modification and treatment on glucose levels and disease symptoms [63]. Results of trials demonstrated that TIR may be used as a promising metric in assessing glycemic control and the prognosis of diabetes complications development [74, 75].

CAN is one of the frequent long-term complications of DM, and reasonable control of GV may be necessary for its prevention. Determination of GV may have advantages for predicting future complications of DM in clinical trials and practice. The association of ANS dysfunction and glucose levels, insulin resistance, and HbA1c variability suggest further research to reduce chronic complications development. Further investigation is needed to study the mechanisms of GV and evaluate them as therapeutic targets in the treatment of patients with T2DM.

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Варіабельність глікемії та діабетична кардіальна автономна нейропатія

Резюме. Кардіальна автономна нейропатія (КАН) тісно пов’язана з приблизно п’ятикратним підвищенням ризику серцево-судинної смертності у хворих на цукровий діабет (ЦД). Ураження вегетативної функції при ЦД, що призводить до розвитку КАН, може супроводжуватися ішемією коронарних артерій, порушеннями серцевого ритму, «тихим» інфарктом міокарда, вираженим ортостатичним катараксом та синдромом раптової серцевої смерті. В огляді наведено аналіз літературних даних щодо впливу варіабельності глікемії на розвиток діабетичної КАН. Проаналізовано можливі взаємозв’язки між показниками варіабельності глікемії (ВГ) та діабетичною КАН. Незадовільний глікемічний контроль та неконтрольований глікемічний статус вважаються основними чинниками ризику хронічних ускладнень ЦД. Збільшення ВГ асоціюється з вищим ризиком хронічних ускладнень ЦД, серцево-судинним риском, синдромом раптової серцевої смерті та вираженою ортостатичною гіпотензією. Результати клінічних досліджень підтвердили, що варіабельність глікемії може мати переваги щодо прогнозування подальших ускладнень ЦД у клінічних дослідженнях і на практиці.

Ключові слова: варіабельність глікемії, кардиальна автономна нейропатія, цукровий діабет.