Heart, Lung and Circulation (2019) **28,** 553–559
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.10.019

REVIEW

Glucose Variability and Coronary Artery Disease

Jinggang Xia, PhD *, **Chunlin Yin, PhD** **

Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing, 100053, China

Received 9 April 2018; received in revised form 29 August 2018; accepted 8 October 2018; online published-ahead-of-print 12 November 2018

Fasting blood glucose, postprandial blood glucose and glycated haemoglobin are considered three important indicators for diabetes treatment. There is increasing evidence that glucose variability has more detrimental effects on the coronary arteries than does chronic sustained hyperglycaemia. This overview summarises recent findings in the field of glucose variability and its possible relationship with coronary artery disease. Glucose variability may be a marker of increased progression of coronary disease and plaque vulnerability. It might be a potential new therapeutic target for secondary prevention of coronary artery disease. Future studies will focus on the early detection and control of glucose variability to improve the clinical outcomes in patients with coronary artery disease.

Keywords Glucose variability • Coronary artery disease • Outcome

Introduction

Worldwide, the number of people with type 2 diabetes mellitus (T2DM) is increasing. Diabetes mellitus (DM) is associated with vascular changes, especially coronary artery disease (CAD), leading to acute myocardial infarction (AMI) and ischaemic heart failure. Presently, the use of second-generation everolimus-eluting stents (EES) in percutaneous coronary interventions (PCI) has improved outcomes in the treatment of CAD across many patient populations, including those with DM [1]. However, patients with diabetes mellitus (DM) are at a particularly higher risk for restenosis, late stent thrombosis and target lesion revascularisation than patients without DM [2,3]. The study by Tanaka et al. showed that neointimal coverage and neointimal thickness were higher in DM patients than in non-DM patients at 9 months after sirolimus-eluting stent implantation [4]. The study from Sakata et al. showed that the follow-up lumen in DM patients appears to be determined primarily by the smaller lumen at the postprocedure rather than exaggerated neointima within the stent or plaque proliferation at the reference segments [5]. In contrast, the study from Iwasaki et al. showed that EES provided a similar level of average neointimal thickness and coverage in both diabetic and nondiabetic patients but that uneven neointimal suppression occurred in the diabetic patients [6]. Optimising control of blood glucose is the main way to improve the prognosis of CAD. Fasting blood glucose, postprandial blood glucose and glycated haemoglobin (HbA1c) are considered three important indicators for diabetes treatment [7]. The HbA1c-centric approach has promoted studies with aggressive treatment goals, such as ACCORD and VADT. These studies have demonstrated both the limitations of HbA1c and the underestimation of the deleterious effect of hypoglycaemia on cardiovascular outcomes [8]. It is well recognised that significant excursions in blood glucose – both upward and downward – might not be adequately reflected in HbA1c [9]. T2DM patients with similar HbA1c values, for example, can have markedly different daily glucose profiles with variations in both the frequency and duration of glucose excursions [10]. Glucose variability (GV) is emerging as an important dynamic parameter of diabetes control [11]. There is increasing evidence that GV has more detrimental effects on the coronary arteries than does chronic sustained hyperglycaemia [12].

*Corresponding author. Tel.: +8613621041267; Fax: +86 10 83198252. Email: xiajinggang@sina.cn
**Corresponding author. Email: yinclmail@163.com

Parameter Evaluation of GV

The utility of GV in clinical practice is hotly debated [13]. It also remains unclear which method for measuring GV is most robust for predicting outcomes [14].

The parameters of GV include the standard deviation of blood glucose (SDBG), the mean amplitude of glycaemic excursions (MAGE), the coefficient of glucose variation, the mean of daily differences (MODD), the SD of fasting blood glucose and the SD of glycosylated haemoglobin. The SDBG, MAGE and coefficient of glucose variation values are used for the assessment of within-day GV. The MODD, SD of fasting blood glucose and SD of HbA1c values are used for the assessment of day-to-day or longer GV assessment. SDBG is the most widely used parameter of intraday GV. It has the advantages of easy access to data, wide coverage, small economic burden and no limit of application, especially for outpatients. The disadvantage is that we can only evaluate the extent of the deviation of the total blood glucose; we cannot distinguish small variations in GV or analyse the frequency of GV, so the extent of organ damage cannot be evaluated. MAGE, which represents only major excursions from the mean and ignores excursions of <1 SD, was also used as an intraday GV parameter [15]. MAGE was calculated as described by Service et al. [16] by measuring the arithmetic mean of differences between consecutive peaks and nadirs as long as the differences were greater than the standard deviation around the mean glucose level. An automated algorithm has been created for this calculation. With the clinical application of the continuous glucose monitoring system (CGMS), MAGE is gradually becoming the gold standard for evaluating GV [12,17]. However, because MAGE represents only major excursions from the mean and ignores excursions of <1 SD, this approach disregards smaller excursions that may be important [18]. The coefficient of glucose variation is calculated by dividing the SD by the mean blood glucose. It also reflects the within-day glucose variability.

MODD measures between-day variability. It is the average of the differences between blood glucose values measured at the same time on consecutive days. The measurement requires a large number of data points and software to perform the calculations. There is a high degree of correlation between the SD of fasting blood glucose and MODD [17,18]. The values of fasting blood glucose levels within a few weeks or a few months are used to calculate the SD of fasting blood glucose. The values of HbA1c levels within a few months or a few years are used to calculate the SD of HbA1c. Therefore, the SD of fasting blood glucose and the SD of HbA1c are used for the assessment of long-term GV.

Association Between GV and CAD

A recent study suggested that there was a close relationship between GV and CAD. Glucose variability may be a marker of increased progression of coronary disease and plaque vulnerability (Table 1).

As early as 2007, Mita et al. [19] investigated the effect of fluctuations in blood glucose levels on atherogenesis. Apolipoprotein (apo) E-deficient mice fed maltose twice daily were used as a model of repetitive postprandial glucose spikes. The authors investigated the number of macrophages that adhered to the endothelium and the area of fibrotic arteriosclerotic lesions with and without administration of miglitol, an α-glucosidase inhibitor. The results showed that GV accelerates atherogenesis. The acceleration was independent of changes in serum cholesterol levels in vivo. Reduction in GV by an α-glucosidase inhibitor efficiently controlled the progression of atherosclerosis. Tang et al. [17] identified the relationship between GV and the 10-year risk of CAD in T2DM patients with good glycaemic control. The results showed that increased MAGE was an independent predictor of high 10-year CAD risk. It was concluded that GV independently predicts the 10-year CAD risk in T2DM patients with well-controlled HbA1c.

Kuroda et al. [20] investigated the association between GV and coronary plaque morphology in CAD patients. A total of 72 consecutive CAD patients receiving adequate lipid-lowering therapy were enrolled. The results identified MAGE as the only independent predictor of the presence of thin-cap fibroatheroma (TCFA). They concluded that GV and hypoglycaemia may impact the formation of lipid-rich plaques and the thinning of fibrous caps in CAD patients treated with lipid-lowering therapies. Nusca et al. [21] found that higher GV has been associated with worse postprocedural creatinine and neutrophil gelatinase-associated lipocalin variations. They also found that GV was increased in patients with periprocedural myocardial infarction. Kuroda et al. [22] investigated the effects of GV on neointimal growth after EES implantation. Compared to non-major adverse cardiovascular events (non-MACE) cases, cases of MACE exhibited a significantly higher MAGE, maximum neointimal thickness (NIT), and variability in NIT at the 9-month follow-up, although there were no significant differences in these groups' HbA1c and lipid levels. The study suggested that GV may affect vessel healing after EES implantation in patients with CAD who are receiving lipid-lowering therapy. Our previous study also obtained similar results that showed that a higher GV was correlated with a higher incidence of periprocedural myocardial infarction and MACE after coronary intervention at the 6-month follow-up [23]. Our animal study also showed that a higher GV was associated with a higher percentage diameter stenosis, late loss, percentage area stenosis, and NIT after stent implantation by optical coherence tomography in a diabetic/hypercholesterolaemic swine model [24].

The correlations of GV with the target lesion, the non-target lesion, the left ventricular remodelling (LVR) and the outcome of acute coronary syndrome (ACS) were also reported. Okada et al. [25] investigated the association between GV and coronary plaque tissue characteristics in 57 patients with ACS. They found that higher GV as measured by CGMS was independently and more strongly associated with increased lipid and decreased fibrous contents

Table 1 **Published articles confirming association between glucose variability and coronary artery disease.**

Relation with glucose variability	Study, Year	Animal/ Human	Study size	Duration	Findings
Cardiovascular risk	Tang et al. 2016 [17]	Human	240	10 year	Glycaemic variability predicts independently the 10-y cardiovascular disease risk of type 2 diabetes mellitus patients with well-controlled HbA1c
Atherogenesis	Mita et al. 2007 [19]	Mice	67	11 weeks	Fluctuations in blood glucose levels accelerated macrophage adhesion and the size of arteriosclerotic lesion in vivo
Coronary plaque and neointimal	Kuroda et al. 2015 [20]	Human	72	During hospitalisation	Glucose fluctuation and hypoglycaemia may impact the formation of lipid-rich plaques and thinning of fibrous cap in coronary artery disease patients with lipid-lowering therapy
Coronary plaque and neointimal	Kuroda et al. 2016 [22]	Human	50	9 months	Glucose fluctuation may affect vessel healing after everolimus-eluting stent implantation in patients with coronary artery disease who are receiving lipid-lowering therapy
Coronary plaque and neointimal	Xia et al. 2017 [24]	Swine	24	28 days	The extent of glucose fluctuation may be related to the degree of neointimal proliferation
Coronary plaque and neointimal	Okada et al. 2015 [25]	Human	57	During hospitalisation	Higher blood glucose variability was an independent determinant of increased lipid and decreased fibrous contents with larger plaque burden
Coronary plaque and neointimal	Gohbara et al. 2016 [26]	Human	46	During hospitalisation	Higher glucose fluctuation after the onset of first-episode acute coronary syndrome was correlated with thinner fibrous cap thickness and higher prevalence of thin-cap fibroatheroma at the non-culprit plaque in the non-culprit vessel.
Periprocedural myocardial infarction	Nusca et al. 2015 [21]	Human	28	During hospitalisation	Glucose fluctuation has been observed to increase in patients with periprocedural myocardial infarction
Left ventricular remodelling	Teraguchi et al. 2014 [27]	Human	36	During hospitalisation	Glycaemic variability is associated with impairment of myocardial salvage in patients with successful recanalisation of myocardial infarction
Left ventricular remodelling	Gohbara et al. 2015 [29]	Human	69	7 months	Higher glycaemic variability could be the cause of left ventricular remodelling in the chronic phase in patients with acute myocardial infarction regardless of the level of HbA1c

Table 1. (continued).

Relation with glucose variability	Study, Year	Animal/ Human	Study size	Duration	Findings
Major adverse cardiovascular events	Xia et al. 2017 [23]	Human	746	6 months	Higher blood glucose variability was correlated with higher incidence of periprocedural myocardial infarction and major adverse cardiovascular events at 6 months follow-up
Major adverse cardiovascular events	Tokue et al. 2015 [30]	Human	103	During hospitalisation	Higher glycaemic variability had an adverse impact on major adverse cardiac and cerebrovascular events after ST-elevated myocardial infarction
Major adverse cardiovascular events	Xia et al. 2017 [31]	Human	864	30 days	Higher glucose variability was correlated with higher incidence of major adverse cardiac and cerebrovascular events, atrial fibrillation and longer length of stay in patients with acute coronary syndrome

with a larger plaque burden and a higher remodelling index in the culprit vessel of ACS patients. Gohbara et al. [26] found that higher MAGE measured early after the onset of first-episode ACS correlated with thinner fibrous cap thickness and higher prevalence of TCFA at the non-culprit plaque in the non-culprit vessel. Teraguchi et al. [27] investigated the impact of GV on myocardial salvage following successful recanalisation of primary AMI and found that MAGE was significantly negatively correlated with the myocardial salvage index. A recent study showed that, early after the onset of AMI, MAGE identified patients with LVR in the chronic phase regardless of the level of HbA1c [28,29]. Tokue et al. found that in patients, an intermittent hyperglycaemic pattern but not a persistent hyperglycaemic pattern had an adverse impact on major adverse cardiac and cerebrovascular events (MACCE) [30]. Our previous study also showed that higher GV was correlated with a higher incidence of atrial fibrillation, a longer length of stay and MACCE in patients with ACS during the 30-day follow-up [31].

Pathogenic Mechanism of GV

The mechanism of coronary artery damage caused by GV has not yet been elucidated.

High glucose concentration increases oxidative stress by driving overproduction of the superoxide radical in the mitochondria [32]. Transient high glucose spikes cause higher oxidative stress than sustained chronic hyperglycaemia [33–35]. The key role of oxidative stress in the development of coronary artery endothelial damage is well known [36,37] (Figure 1). Glucose variability impairs endothelial function in both the macrovascular and microvascular beds [38–41]. A combination of glucotoxicity and lipotoxicity increased reactive oxygen species (ROS)

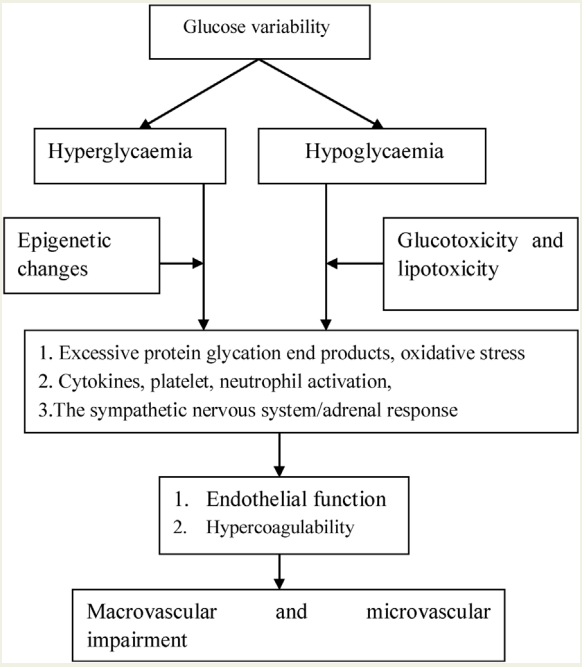

Figure 1 Pathogenic mechanism of glucose variability.

production in mitochondria and caused further deterioration of endothelial function [42]. Therefore, GV is considered an important factor in the development of endothelial dysfunction and the subsequent changes in vascular wall morphology [8].

Advanced glycation end products (AGEs) have been shown to contribute to the development and progression of diabetes-related complications. Cross-linking of proteins by AGE modification not only leads to an increase in vascular and myocardial stiffness but also deteriorates structural integrity and physiological function of multiple organ systems, thus being involved in isolated systolic hypertension and diastolic heart failure [43]. Higher GV might cause more oxidative stress by activating more AGEs. There is a growing body of evidence suggesting that atherosclerosis is an inflammatory disease. Activation of AGEs results in the generation of intracellular oxidative stress and the subsequent activation of NF-κB in vascular wall cells, which could promote the expression of a variety of atherosclerosis/inflammation-related genes, thereby contributing to the development and progression of CAD in diabetes patients [44].

Glucose variability might have an important effect on neutrophil activation, platelet activation and cytokines. Abnormal neutrophil activation and platelet function represent the main determinants of vascular accidents in diabetic patients, contributing to high inflammatory reactions and a high incidence of thrombotic events [45]. Hyperglycaemia induces neutrophil and platelet activation and increases reactive oxygen species production, playing an important role in the development of vascular damage. A recent study has also shown that acute glucose fluctuation may cause interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and intercellular adhesion molecule-1 (ICAM-1) levels, resulting in severe cardiovascular injury [46].

Glucose variability is the range of glucose fluctuation between hyperglycaemia and hypoglycaemia. ''Excellent'' diabetes control, as expressed by close to normal HbA1c, increases the risk of hypoglycaemia when associated with high glucose variability and may therefore be dangerous. The danger comes not only from the acute consequences of hypoglycaemic episodes but also from the induction of pathogenic mechanisms that then lead to diabetic vascular complications. Hypoglycaemia in Type 1 diabetic patients without cardiovascular disease is significantly associated with an impaired pattern of heart rate variability [47]. Studies have shown that hypoglycaemia is also associated with increased short- and long-term mortality in AMI patients [48]. Although the mechanism by which hypoglycaemia leads to increased mortality is not clear, an abnormal QT prolongation during severe hypoglycaemia may be associated with the increased 30-day mortality. In experimentally induced hypoglycaemia, potentially fatal abnormal QT prolongation, sinus bradycardia, and ventricular arrhythmias occurred [49]. A clinical study described bradycardia during severe hypoglycaemia in both diabetic and non-diabetic patients, which may reflect an imbalance of the sympathetic nervous system [50].

Treatment of GV

There is currently no effective treatment to reduce GV. Coronary artery disease is a multifactorial disease. Whether reducing GV can improve the prognosis of CAD is still unknown.

Basic measures for controlling GV include diet, weight reduction and exercise. T2DM is intrinsically linked with lifestyle factors, including obesity and other dietary factors amenable to nutrition therapy. Glucose variability may therefore be influenced by energy restriction for weight loss and dietary factors that can assist in optimising glycaemic control [51]. Some studies provide preliminary evidence that GV can be modified by altering carbohydrate quality, quantity, or distribution, as well as by altering protein and fibre intake, and should be considered for optimising blood glucose control; however, the majority of studies were uncontrolled, with small sample sizes and short intervention durations [52–54]. The physical activity of the patient is an important aspect that determines the use of energy substrates. In patients with T2DM, low/medium intensity aerobic exercise (25–50% VO_2 max) promotes the consumption of fatty acids. In the often elderly population, prescription of physical activity must consider the characteristics of the individual, such as fitness, degree of training, muscle mass and the presence of microvascular and macrovascular complications [55].

Large-scale, randomised controlled trials of drug therapy specifically aimed at correcting GV are lacking. Trials that prevent T2DM and target postprandial glucose (PPG) levels have been conducted, and PPG excursions play an important role in determining the overall control and the extent of GV. There is strong epidemiological evidence that PPG levels independently predict CAD events, and evidence that fasting plasma glucose levels are predictive is much weaker [56]. The STOP-NIDDM trial (The Study to Prevent NIDDM (Non-Independent Diabetes Mellitus) trial) [57] and the ACE trial [58] showed that acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay the development of type 2 diabetes in patients with impaired glucose tolerance. The NAVIGATOR trial also showed that the use of valsartan for 5 years, along with lifestyle modification, led to a 14% relative reduction in the incidence of diabetes among patients with impaired glucose tolerance and cardiovascular disease or risk factors [59]. However, there is currently no good evidence that targeting PPG results in reduced cardiovascular complications.

Studies focussing on reducing GV are currently limited to small sample sizes and single centres. The study by Klein et al. [60] showed that the metabolic effect of the albumin-bound insulin analogues insulin detemir and NN344 significantly lowered GV in comparison to insulin glargine in individuals with type 2 diabetes. The post hoc analysis from King et al. [61] examined GV and the proportion of subjects achieving recommended blood glucose targets with the fixed ratio combination of insulin degludec and liraglutide (IDegLira) compared to insulin degludec (IDeg) or liraglutide alone. They found that treatment with IDegLira allows more patients with T2DM to maintain their blood glucose

within target ranges throughout the day than either IDeg or liraglutide alone. The study by Nomoto et al. [62] investigated the superiority of dapagliflozin on GV compared with DPP-4 inhibitors in patients with T2DM on insulin using the CGMS. They found that combination therapy of dapagliflozin and insulin was not superior in controlling glucose fluctuation when compared to DPP-4 inhibitors. However, dapagliflozin may, in part, provide favourable effects on metabolism in patients with T2DM treated with insulin therapy. The ability to undertake these studies is facilitated by the availability and continued development of CGMS technology, which provides an objective and comprehensive glucose monitoring tool for measuring GV modifications arising from treatments that target GV. The latest study from Shimabukuro et al. [63] aimed to evaluate the short-term effects of GV on heart rate variability and sympathetic nervous system activity in T2DM patients with recent ACS. They also examined the effect of suppressing glucose variability with miglitol on these variables. It was a prospective, randomised, open-label, blinded-endpoint, multicentre, parallel-group comparative study in 39 T2DM patients. They found that GV was associated with alterations in heart rate variability and sympathetic nervous system activity, which were mitigated by miglitol.

Conclusions

Glucose variability, fasting blood glucose, postprandial blood glucose and HbA1c are considered four important indicators for diabetes treatment. GV has been recognised as a residual risk apart from hypertension, dyslipidaemia and smoking for the development of CAD. GV may be a marker for increased progression of coronary disease and plaque vulnerability. It might be a potential new therapeutic target for secondary prevention of CAD. Future studies will focus on early detection, assessment, and potential medication and lifestyle interventions to improve the clinical outcome of patients with CAD. Multicentre, randomised controlled trials to clarify whether early interventions to reduce GV can improve clinical outcomes still need to be conducted.

Disclosures

The authors declare that there are no conflicts of interest.

Acknowledgement

This research was supported by the National Natural Science Foundation of China (No. 81770344) and the China young and middle-aged clinical research -VG fund (No. 2017-CCA-VG-043).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.10.019.

References

[1] Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. Eurointervention 2006;2:286–94.
[2] Machecourt J, Danchin N, Lablanche JM, Fauvel JM, Bonnet JL, Marliere S, et al. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. J Am Coll Cardiol 2007;50:501–8.
[3] Hong SJ, Kim MH, Ahn TH, Ahn YK, Bae JH, Shim WJ, et al. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. Heart 2006;92:1119–24.
[4] Tanaka N, Terashima M, Rathore S, Itoh T, Habara M, Nasu K, et al. Different patterns of vascular response between patients with or without diabetes mellitus after drug-eluting stent implantation: optical coherence tomographic analysis. Jacc Cardiovasc Interv 2010;3:1074–9.
[5] Sakata K, Waseda K, Kume T, Otake H, Nakatani D, Yock PG, et al. Impact of diabetes mellitus on vessel response in the drug-eluting stent era pooled volumetric intravascular ultrasound analyses. Circ Cardiovasc Interv 2012;5:763–71.
[6] Iwasaki M, Otake H, Shinke T, Nakagawa M, Hariki H, Osue T, et al. Vascular responses in patients with and without diabetes mellitus after everolimus-eluting stent implantation. Circ J 2014;78:2188–96.
[7] Valensi P, Husemoen L, Weatherall J, Monnier L. Association of postprandial and fasting plasma glucose with HbA1c across the spectrum of glycaemic impairment in type 2 diabetes. Int J Clin Pract 2017;71.
[8] krha J, oupal J, krha Jr J, Prázný M. Glucose variability, HbA1c and microvascular complications. Rev Endocr Metab Disord 2016;17:1–8.
[9] Ceriello A, Ihnat MA. 'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting. Diabet Med 2010;26:222–5.
[10] Siegelaar SE, Holleman F, Hoekstra JB, DeVries JH. Glucose variability; does it matter? Endocr Rev 2010;31:171.
[11] Farkouh ME. Blood glucose variability: a new metric for interventional cardiology? Jacc Cardiovasc Interv 2015;8:812.
[12] Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y, et al. Effect of daily glucose fluctuation on coronary plaque vulnerability in patients pre-treated with lipid-lowering therapy: a prospective observational study. Jacc Cardiovasc Interv 2015;8:800.
[13] Devries JH. Glucose variability where it is important and how to measure it. Diabetes 2013;62:1405.
[14] Inzucchi SE, Umpierrez G, Digenio A, Zhou R, Kovatchev B. How well do glucose variability measures predict patient glycaemic outcomes during treatment intensification in type 2 diabetes? Diabetes Res Clin Pract 2015;108:179.
[15] Service FJ. Glucose variability. Diabetes 2013;62:1398–404.
[16] Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19:644.
[17] Tang X, Li S, Wang Y, Wang M, Yin Q, Mu P, et al. Glycemic variability evaluated by continuous glucose monitoring system is associated with the 10-y cardiovascular risk of diabetic patients with well-controlled HbA1c. Clin Chim Acta 2016;461:146.
[18] Jung HS. Clinical implications of glucose variability: chronic complications of diabetes. Endocrinol Metab (Seoul) 2015;30:167–74.
[19] Mita T, Otsuka A, Azuma K, Uchida T, Ogihara T, Fujitani Y, et al. Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E-deficient mice. Biochem Biophys Res Commun 2007;358:679–85.
[20] Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y, et al. Association between daily glucose fluctuation and coronary plaque properties in patients receiving adequate lipid-lowering therapy assessed by continuous glucose monitoring and optical coherence tomography. Cardiovasc Diabetol 2015;14:78.
[21] Nusca A, Lauria PA, Melfi R, Proscia C, Maddaloni E, Contuzzi R, et al. Glycemic Variability assessed by continuous glucose monitoring and short-term outcome in diabetic patients undergoing percutaneous coronary intervention: an observational pilot study. J Diabetes Res 2015;2015:250201.
[22] Kuroda M, Shinke T, Otake H, Sugiyama D, Takaya T, Takahashi H, et al. Effects of daily glucose fluctuations on the healing response to everolimus-eluting stent implantation as assessed using continuous glucose monitoring and optical coherence tomography. Cardiovasc Diabetol 2016;15:79.
[23] Xia J, Xu J, Hu S, Hao H, Yin C, Xu D. Impact of glycemic variability on the occurrence of periprocedural myocardial infarction and major

adverse cardiovascular events (MACE) after coronary intervention in patients with stable angina pectoris at 6months follow-up. Clin Chim Acta 2017;471:196–200.
[24] Xia J, Qu Y, Yin C, Xu D. Optical coherence tomography assessment of glucose fluctuation impact on the neointimal proliferation after stent implantation in a diabetic/hypercholesterolemic swine model. Int Heart J 2017;58.
[25] Okada K, Hibi K, Gohbara M, Kataoka S, Takano K, Akiyama E, et al. Association between blood glucose variability and coronary plaque instability in patients with acute coronary syndromes. Cardiovasc Diabetol 2015;14:111.
[26] Gohbara M, Hibi K, Mitsuhashi T, Maejima N, Iwahashi N, Kataoka S, et al. Glycemic variability on continuous glucose monitoring system correlates with non-culprit vessel coronary plaque vulnerability in patients with first-episode acute coronary syndrome — optical coherence tomography study. Circ J 2015;80:111–25.
[27] Teraguchi I, Imanishi T, Ozaki Y, Tanimoto T, Ueyama M, Orii M, et al. Acute-phase glucose fluctuation is negatively correlated with myocardial salvage after acute myocardial infarction. Circ J 2014;78:170.
[28] Natsuaki M, Node K. Glycemic variability and cardiac remodeling in patients with acute myocardial infarction. Circ J 2015;79:972–3.
[29] Gohbara M, Iwahashi N, Kataoka S, Hayakawa Y, Sakamaki K, Akiyama E, et al. Glycemic variability determined by continuous glucose monitoring system predicts left ventricular remodeling in patients with a first ST-segment elevation myocardial infarction. Circ J 2015;79:1092–9.
[30] Tokue M, Iijima R, Imamura T, Niikura H, Hayashi F, Yazaki Y, et al. Impact of glycemic variability in patients with ST-elevated myocardial infarction. Int J Cardiol 2015;187:660–2.
[31] Xia J, Xu J, Li B, Liu Z, Hao H, Yin C, et al. Association between glycemic variability and major adverse cardiovascular and cerebrovascular events (MACCE) in patients with acute coronary syndrome during 30-day follow-up. Clin Chim Acta 2017;466:162–6.
[32] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–25.
[33] Elosta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med 2008;205:2409–17.
[34] Salisbury D, Bronas U. Reactive oxygen and nitrogen species: impact on endothelial dysfunction. Nurs Res 2015;64:53–66.
[35] Wang L, Wang J, Fang J, Zhou H, Liu X, Su SB. High glucose induces and activates Toll-like receptor 4 in endothelial cells of diabetic retinopathy. Diabetol Metab Syndr 2015;7:89.
[36] De Nigris V, Pujadas G, La Sala L, Testa R, Genovese S, Ceriello A. Short-term high glucose exposure impairs insulin signaling in endothelial cells. Cardiovasc Diabetol 2015;14:114.
[37] Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–7.
[38] Zhang XG, Zhang YQ, Zhao DK, Wu JX, Zhao J, Jiao XM, et al. Relationship between blood glucose fluctuation and macrovascular endothelial dysfunction in type 2 diabetic patients with coronary heart disease. Eur Rev Med Pharmacol Sci 2014;18:3593–600.
[39] Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349–54.
[40] Schisano B, Tripathi G, McGee K, McTernan PG, Ceriello A. Glucose oscillations, more than constant high glucose, induce p53activation and a metabolic memory in human endothelial cells. Diabetologia 2011;54:1219–26.
[41] Pena AS, Couper JJ, Harrington J, Gent R, Fairchild J, Tham E, et al. Hypoglycemia, but not glucose variability, relates to vascular function in children with type 1 diabetes. Diabetes Technol Ther 2012;14:457–62.
[42] Kumar B, Kowluru A, Kowluru RA. Lipotoxicity augments glucotoxicity-induced mitochondrial damage in the development of diabetic retinopathy. Invest Ophthalmol Vis Sci 2015;56:2985–92.
[43] Yamagishi S, Fukami K, Matsui T. Crosstalk between advanced glycation end products (AGEs)-receptor RAGE axis and dipeptidyl peptidase-4-incretin system in diabetic vascular complications. Cardiovasc Diabetol 2015;14:1–12.
[44] Rhee SY, Kim YS. The role of advanced glycation end products in diabetic vascular complications. Diabetes Metab J 2018;42:188.
[45] Schiattarella GG, Carrizzo A, Ilardi F, Damato A, Ambrosio M, Madonna M, et al. Rac1 modulates endothelial function and platelet aggregation in diabetes mellitus. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 2018;7:e007322.
[46] Wu N, Shen H, Liu H, Wang Y, Bai Y, Han P, et al. Acute blood glucose fluctuation enhances rat aorta endothelial cell apoptosis, oxidative stress and pro-inflammatory cytokine expression in vivo. Cardiovasc Diabetol 2016;15:109.
[47] Chow E, Bernjak A, Walkinshaw E, Lubina-Solomon A, Freeman J, et al. Cardiac autonomic regulation and repolarization during acute experimental hypoglycemia in type 2 diabetes. Diabetes 2017;66:db161310.
[48] Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction defining the optimal outcomes-based measure of risk. Circulation 2008;117:1018–27.
[49] Chow E, Bernjak A, Williams S, Fawdry RA, Hibbert S, Freeman J, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–47.
[50] Reno CM, Daphnaiken D, Chen YS, VanderWeele J, Jethi K, Fisher SJ. Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. Diabetes 2013;62:3570–81.
[51] Tay J, Thompson CH, Brinkworth GD. Glycemic variability assessing glycemia differently and the implications for dietary management of diabetes. Annu Rev Nutr 2015;35:389.
[52] Mori Y, Ohta T, Yokoyama J, Utsunomiya K. Effects of low-carbohydrate/high-monounsaturated fatty acid liquid diets on diurnal glucose variability and insulin dose in type 2 diabetes patients on tube feeding who require insulin therapy. Diabetes Technol Ther 2013;15:762–7.
[53] Hernandez TL, Van Pelt RE, Anderson MA, Daniels LJ, West NA, Donahoo WT, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. Diabetes Care 2014;37:1254–62.
[54] Pearce KL, Noakes M, Keogh J, Clifton PM. Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. Am J Clin Nutr 2008;87:638.
[55] Zenari L, Marangoni A. What are the preferred strategies for control of glycaemic variability in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2013;15:17–25.
[56] Meigs JB, Nathan DM, D'Agostino Sr RB, Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: the framingham offspring study. Diabetes Care 2002;25:1845–50.
[57] Chiasson JL. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–7.
[58] Holman RR, Coleman RL, Chan J, Chiasson JL, Feng H, Ge J, et al. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5.
[59] Luan FL. Effect of valsartan on the incidence of diabetes. N Engl J Med 2010;363:792–3.
[60] Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes Metab 2010;9:290–9.
[61] King AB, Philistsimikas A, Kilpatrick ES, Langbakke IH, Begtrup K, Vilsbøll T. A Fixed Ratio Combination of Insulin Degludec and Liraglutide (IDegLira) Reduces Glycemic Fluctuation and Brings More Patients with Type 2 Diabetes Within Blood Glucose Target Ranges. Diabetes Technol Ther 2017;19:255–64.
[62] Nomoto H, Miyoshi H, Sugawara H, Ono K, Yanagiya S, Oita M, et al. A randomized controlled trial comparing the effects of dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin. Diabetol Metab Syndr 2017;9:54.
[63] Shimabukuro M, Tanaka A, Sata M, Dai K, Shibata Y, Inoue Y, et al. α-Glucosidase inhibitor miglitol attenuates glucose fluctuation, heart rate variability and sympathetic activity in patients with type 2 diabetes and acute coronary syndrome: a multicenter randomized controlled (MACS) study. Cardiovasc Diabetol 2017;16:86.