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Endothelial Dysfunction and Platelet Hyperactivation in Diabetic Complications Induced by Glycemic Variability

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ABSTRACT

The development and progression of the complications of chronic diabetes mellitus are attributed not only to increased blood glucose levels but also to glycemic variability. Therefore, a deeper understanding of the role of glycemic variability in the development of diabetic complications may provide more insight into targeted clinical treatment strategies in the future. Previously, the mechanisms implicated in glycemic variability-induced diabetic complications have been comprehensively discussed. However, endothelial dysfunction and platelet hyperactivation, which are two newly recognized critical pathogenic factors, have not been fully elucidated yet. In this review, we first evaluate the assessment of glycemic variability and then summarise the roles of endothelial dysfunction and platelet hyperactivation in glycemic variability-induced complications of diabetes, highlighting the molecular mechanisms involved and their interconnections.

Introduction

Diabetes mellitus (DM) is the third most common chronic disease worldwide and a serious threat to human health and life [1]. DM-related macrovascular and microvascular complications, including coronary heart disease, cerebrovascular disease, heart failure, peripheral vascular disease, diabetic retinopathy (DR), neuropathy, and nephropathy, impair the quality of life and cause disability and premature death [2].

Fasting plasma glucose (FPG), postprandial glucose excursions, and hemoglobin A1c (HbA1c), described as the "glucose triad," are the main parameters used in monitoring patients with type 2 diabetes (T2D) [3]. Among elderly patients with T2D, all-cause mortality [4], including cardiovascular disease mortality [5], is mainly related to the variability or instability of fasting glycemia rather than its absolute values. In the Veteran Affairs Diabetes Trial, longitudinal variations in FPG were associated with all-cause mortality, even when accounting for standard measures of glucose control, as well as comorbidity and lifestyle factors [6]. Notably, many studies have found that HbA1c does not fully explain the risk of chronic complications of T2D. Therefore, other reliable and accurate monitoring parameters of diabetic complications need to be explored.

Good glucose control is one of the most effective means to prevent the complications of advanced DM [7]. Impaired glucose homeostasis is the main risk factor for cardiovascular disease [8]; thus, glycemic variability (GV) might be as important as the glucose triad [9]. Additionally, several studies have confirmed that patients with

DM and fluctuant hyperglycemia have higher risks of chronic vascular complications than those with persistent hyperglycemia [10, 11]. Furthermore, greater degrees of glycemic fluctuation are associated with a higher incidence of complications and worse prognosis [12]. Thus, GV has become a research hotspot in the field of DM prevention and treatment.

Hyperglycemia fluctuation is an important factor that causes aggravation of DM-associated vascular complications. Vascular endothelial dysfunction is the initiating factor for the development of atherosclerosis and is an important pathophysiological basis for diabetic vascular disease. Platelet hyperactivation induced by thrombosis is also essential in the development of vascular events. Furthermore, both increased platelet reactivity and endothelial dysfunction are considered a "prothrombotic state" in DM [13]. This review aimed to provide a deeper understanding of the role and mechanism of GV-induced diabetic complications. Toward this goal, we focused on the relationship between endothelial dysfunction, platelet hyperactivation, and GV.

Indicators of GV

Glucose levels can be measured repeatedly in one day (within-day glucose variability) or during more days (between-day glucose variability) [14]. Another method is continual measurement of glucose levels using a continual glucose monitoring (CGM) system [15].

Dysglycemia in diabetes can be classified into two mechanisms: sustained chronic hyperglycemia and acute fluctuant fluctuations over a daily period [16, 17]. The former is integrated by HbA1c, which depends on both interprandial and postprandial hyperglycemia, and the percentage of each contributor is modulated by the degree of diabetic control [18]. There are many parameters for the clinical evaluation of GV [19], with the most common measures being the following (▶ **Table 1**): (1) assessment of within-day blood glucose variability, including the mean amplitude of glycemic excursions (MAGE), largest amplitude glycemic excursion (LAGE), standard deviation (SD) of all blood glucose measurements, and high/low blood glucose index (HBGI/LBGI); (2) assessment of day-to-day blood glucose variability, including the FPG coefficient of variation (CV), mean of daily difference (MODD), and average daily risk range (ADRR); (3) assessment of postprandial blood glucose fluctuation, such as the mean indices of meal excursions (MIME); and (4) special assessment for islet transplantation of type 1 DM (T1D), such as the lability index (LI).

The development of CGM technology greatly expands the ability to assess glycemic control throughout the day and has enabled research on the influence of acute blood glucose fluctuations in real life [36]. The 2017 Advanced Technologies & Treatments for Diabetes consensus conference [37] identified "time in ranges" as a metric of glycemic control that provides more actionable information than HbA1c alone. The metric includes three key CGM measurements: percentage of readings and time per day within target glucose range [TIR, 70–180 mg/dl (3.9–10.0 mmol/l)], time below target glucose range [TBR, 70 mg/dl (3.9 mmol/l)], and time above target glucose range [TAR, 180 mg/dl (10.0 mmol/)] [38].

These variability parameters are important in selecting the optimal treatment strategies and estimating the risk of chronic DM complications. GV is closely related to diabetic complications and monitoring it could help in controlling or reducing the risk of complications. Therefore, the parameters of both short- and long-term GV should be further explored. Recently, numerous studies have supported the hypothesis that GV acts as an important determinant in both the genesis and development of diabetic vascular complications [39–44].

GV and vascular complications of DM

Diabetic vascular complications are conventionally classified as microvascular and macrovascular according to the size and location of the blood vessels involved [45]. Several studies have demonstrated that the presence of macro- and microvascular complications in patients with DM is related not only to chronic hyperglycemia represented by HbA1c but also to acute glycemic fluctuations [46, 47]. There is substantial evidence supporting that GV has drawn a great attention for its role in macro- and microvascular complications in patients with T1D or T2D [48].

GV and microvascular disease of DM

Microvascular disease, mainly including retinopathy, nephropathy, and neuropathy, is strongly associated with hyperglycemia. Recently, studies have shown a positive association between GV and microvascular complications of diabetes [49]. The present review suggests that increased levels of short-term glucose variability, particularly in FPG levels, may contribute to the development of microvascular complications in T2D, whereas the role of increased short-term glucose variability in the development of microvascular complications in T1D is less evident [50].

Retinopathy

The risk of development and progression of retinopathy has been linked to glycemic exposure in many studies from the Diabetes Control and Complications Trial in 1995 [51]. DR is currently the leading cause of blindness among working-aged persons in the developed world [52]. Many studies in the present literature indicate that short-term GV may contribute to the development or progression of DR in T2D, while long-term GV, represented by HbA1c, appears to play a more important role in retinopathy in patients with T1D or T2D [53]. One study of 415 DR patients with T1D in a tertiary referral centre suggested prevention and early detection of retinopathy in T1D patients, to take HbA1c variability into account when optimizing glycemic control [54].

Nephropathy

In a cross-sectional study of patients with T1D, higher glucose variability, as estimated by SD, CV, and MAGE, was found significantly more often in those with elevated albuminuria than in those with normal albuminuria, although their mean HbA1c was comparable [50]. Moreover, *in vivo* studies have revealed that in patients with T2D, GV results in chronic kidney disease characterized by progressive proteinuria, which ultimately leads to end-stage renal failure [55].

Neuropathy

Many forms of neuropathy can occur, including sensory, motor, and autonomic neuropathies, in the setting of diabetes after the exclusion of other causes. Several retrospective longitudinal studies on patients with T1D have demonstrated that glycemic fluctuations may contribute to diabetic peripheral neuropathy [56] and cardio-

▶ **Table 1** Definition of the various indices used to assess glycemic variability (GV).

Measure [Ref]	Description	Advantages	Limits
Mean amplitude of glycemic excursions (MAGE) [20–22]	Mean of glycemic excursions from nadir to peak blood glucose level and vice versa that are > 1 SD of blood glucose mean	It is a diabetes-specific metric of the amplitude of glucose excursions.	It considers glycemic peaks and nadirs occurring daily but does not account for the total number of fluctuations; it depends on sampling frequency; it is ambiguous as to where peaks and nadirs begin and end.
Largest amplitude glycemic excursion (LAGE) [23]	Maximal sensor glucose levels minus the minimal daily sensor glucose levels	It can reflect variations in the characteristics of within-day and day-to-day blood glucose.	It cannot reflect the frequency of fluctuations or full level of GV for a single day or several days.
Standard deviation (SD) [24–25]	Variation around the mean blood glucose (intra-day or inter-day) [26]	It is a simple, classical statistical method.	It combines information on variability from different sources; it does not address non-Gaussian skewed data.
Coefficient of variation (CV) = SD/mean	Magnitude of variability relative to mean blood glucose [27–28]	It can be used to assign more importance to hypoglycemia than to hyperglycemia.	It is subject to the same limitations as SD. It fails to provide enough weight to hypoglycemic values.
Low blood glucose index (LBGI) [29]	For glucose values < 112.5 mg/dl, average of 27.695 × {[log(glucose)] 1.084 – 5.381}	Heavier weights are assigned to severe hypoglycemic values.	The mathematical form is obscure.
High blood glucose index (HBGI) [30]	For glucose values > 112.5 mg/dl, average of 27.695 × {[log(glucose)] 1.084 – 5.381}	Heavier weights are assigned to severe hyperglycemic values.	The mathematical form is obscure.
Mean of daily difference (MODD) [31]	It is calculated as the average of the absolute difference between values on different days but at the same time for two consecutive days.	It can be used to assess the continuous variability of blood glucose at the same time between different days.	It may be affected by insulin injections.
Average daily risk range (ADRR) [32]	Blood glucose is continuously monitored for 14–28 days at least four times a day. The results are converted to obtain ADRR, which is used to evaluate long-term GV.	It is the best predictor for variations of hypoglycemia and hyperglycemia, independent of the type of diabetes.	Patients are required to master self-monitoring of blood glucose. Because of the high monitoring frequency, long duration, and low patient compliance, this is less frequently applied in clinical practice.
Mean indices of meal excursions (MIME) [33]	These include postprandial spike (PPGE), peak-reaching time, and percentage decrease in blood glucose 1 h after peaking (BR). PPGE is the difference between a postprandial spike and the corresponding preprandial glucose.	Dynamic changes in PPGE can be visually shown in detail.	It is related to mealtime, type of food, and eating style. Changes in postprandial levels during different days cannot be observed.
Lability index (LI) [34]	It is calculated based on changes in glucose levels over time using 4-week glucose records and compared with a clinical assessment of glycemic lability.	It can be used as an indicator of patient prognosis.	It is only applicable to patients with type 1 diabetes mellitus having solitary islet transplantation with recurrent severe hypoglycemia and labile glucose control.
Continuous overall net glycemic action (CONGA-n) [35]	It measures the intraday glycemic swings occurring over predetermined intervals.	It provides an accurate measure of intra-day glycemic variability.	It is difficult to calculate.

vascular autonomic neuropathy [57]. Moreover, high levels of GV, assessed via CGM, appear to have even more deleterious effects than sustained hyperglycemia in the pathogenesis of cardiovascular autonomic neuropathy and other cardiovascular complications in patients with T2D [58, 59].

Both GV, as derived from visit-to-visit FPG measurements using CV, and HbA1c ≥ 53 mmol/mol were potent predictors of diabetic peripheral polyneuropathy (DPN) in patients with T2D. The associations among HbA1c, GV, and DPN suggest a linked pathophysiologic mechanism, which may play a crucial role in clinical risk assessments [60].

GV and macrovascular disease of DM

There are three major manifestations of macrovascular disease: coronary artery disease, cerebrovascular disease, and peripheral artery disease. In patients with T1D and T2D, the role of increased short-term GV in the development of both micro- and macrovascular complications is less evident [50].

Coronary artery disease

DM increases the risk of myocardial infarction (MI) more than any other risk factor aside from cigarette smoking. Coronary artery disease is the most common macrovascular complication recorded in

patients with DM [61]. Fluctuant hyperglycemia has adverse effects on blood vessels that lead to cardiovascular and peripheral vascular diseases. Patients with T2D complicated by coronary heart disease have higher GV than those without coronary heart disease [62]. In addition, increased visit-to-visit GV has been shown to predict mortality in patients with T2D and acute MI [63]. Previous studies have already correlated an increased GV to the occurrence of adverse events in patients with acute coronary syndromes undergoing percutaneous coronary revascularization (PCI) [64, 65].

Cerebrovascular disease

Stroke incidence is elevated in the diabetic population, claiming a high cost in terms of morbidity and mortality [66]. More severe glycemic fluctuations in patients with T2D are associated with a greater risk of cerebral infarction and worse prognoses [67].

Peripheral artery disease

The risk of developing peripheral artery disease (PAD) is increased two- to four-fold in patients with DM compared to those without [68]. One-fourth of patients with PAD demonstrate progression of symptoms over 5 years and a rate of amputation of around 4 %. Diabetes not only affects large-calibre peripheral vessels but distal arterioles as well [66]. A recent large, retrospective cohort study reported that HbA1c and GV, as estimated using FPG-CV, were risk factors for PAD aside from other conventional risk factors in persons with T2D [69].

Endothelial dysfunction in GV induces DM-associated complications

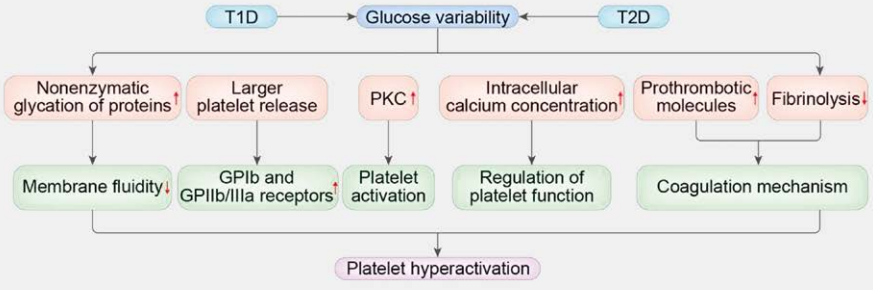
Endothelial dysfunction is defined as a disorder in the capacity of the endothelium to maintain vascular homeostasis [70]. It represents one of the most important determinants of coronary vascular disease [71]. Endothelial dysfunction could contribute to insulin resistance, potentially unifying the etiology of DM and coronary vascular disease [72]. Many studies have confirmed that fluctuant hyperglycemia is more likely to cause vascular endothelial dysfunction than persistent hyperglycemia [73]. Moreover, glucose fluctuation negatively influences endothelial function [74].

Endothelial dysfunction arising from a chronic hyperglycemic state is the result of increased oxidative stress and overproduction of reactive oxygen species (ROS), reduced nitric oxide (NO), and increased expression of adhesion molecules and inflammatory reactions (▶ **Fig. 1**).

Oxidative stress plays a critical role in the pathogenesis of diabetic complications and several vascular diseases [75]. As stated in the unifying theory for DM complications proposed by Brownlee, oxidative stress response accompanied by sharp fluctuations in blood sugar is an important mechanism of vascular endothelial dysfunction [76]. The association between GV and oxidative stress has also been investigated using CGM. Monnier et al. [77] found that the average 24-hour urinary excretion rate of free 8-iso-prostaglandin (PG) F2α, a marker of oxidative stress, in 21 patients with T2D significantly correlated with MAGE, a marker of GV assessed via CGM, and with the area under the curve of the mean postprandial increment of glucose level above preprandial values. This suggests that glycemic fluctuations during postprandial periods are more likely to induce oxidative stress. *In vitro* studies and animal models have also substantiated these results.

Our study found that intermittent high glucose levels (5.56–25 mmol/every 24 h) induced oxidative stress injury with an increase in advanced oxidative protein products (AOPPs) and a decrease in total antioxidant capacity (T-AOC), which led to increased cellular apoptosis in human umbilical vein endothelial cells (HUVECs), compared with a constant high-glucose setting (25 mmol/l). Furthermore, the trend of these indices was verified in streptozotocin (STZ)-induced diabetic rats with fluctuating hyperglycemia treatment [78]. These effects were amplified during glucose fluctuations, consistent with previous observations [79, 80].

NO produced by nitric oxide synthases (NOS) is the smallest gaseous intercellular messenger involved in the modulation of several processes (e. g., blood flow and platelet aggregation control) and is essential for maintaining vascular homeostasis [81]. Aside from being a vasodilator, NO reduces vascular permeability and the synthesis of monocyte and lymphocyte adhesion molecules, which contribute to the reduction of tissue oxidation and inflammation, platelet aggregation, and thrombogenic factor activation. These processes, in turn, lead to the reduction of typical inflammatory processes induced by hyperglycemia [82]. Impaired endothelial NOS activity and enhanced ROS production in DM result in diminished NO bioavailability and vascular damage [83]. Therefore, NO is considered an important anti-atherogenic molecule that is necessary to contain diabetic endothelial alterations [84, 85].



▶ **Fig. 1** Schematic representation of the main processes involved in the pathogenesis of endothelial dysfunction in patients with diabetes with glycemia variability (GV).

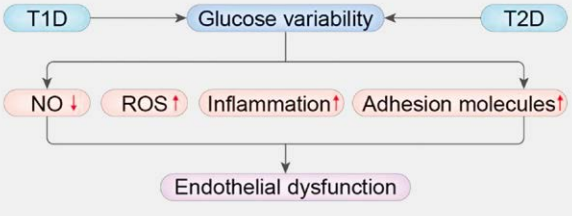
Inflammation is widely considered a key etiological factor that plays a vital role in the development of diabetic complications [86]. Otsuka et al. injected glucose into the intraperitoneal space of Sprague-Dawley rats to cause a temporary increase in blood glucose. The results indicated that a transient increase in blood glucose could induce increased adhesion of monocytes and endothelial cells in the thoracic aorta [87]. Studies by Watada et al. [88] and Mita et al. [89] in rats have also shown that repetitive postprandial hyperglycemia could promote the adhesion of monocytes, macrophages, and aortic endothelial cells more than sustained hyperglycemia, thus increasing the surface area of arteriosclerotic injury. Additionally, studies in HUVECs have also yielded similar results, further confirming that fluctuant hyperglycemia can significantly increase the levels of inflammatory indicators (interleukin-6, tumor necrosis factor-α) and expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) [90–92]. In human circulation, fluctuant hyperglycemia could induce tumour necrosis factor-α production *in vivo*[93]. A previous study showed that high glucose altered the expression profile of cytokines and chemokines via specific signalling pathways and can increase monocyte-endothelial adhesion in monocytes [94]. Acute glucose fluctuation may cause significant oxidative stress and inflammation in rat aortic endothelial cells, increase the adhesion of monocytes to rat aortic endothelial cells, and elevate endothelial cell apoptosis, resulting in severe cardiovascular injury [95].

Platelet hyperactivation in GV-induced DM-associated complications

Increased coagulation, impaired fibrinolysis, and endothelial dysfunction result in a prothrombotic state for which platelet hyperreactivity is said to be an established contributing factor. Complications arise owing to these hyperactive platelets that play a vital role in the pathophysiology of thrombotic events [96].

Platelets could both trigger thrombus formation and release oxidative, mitogenic, and vasoconstrictive substances that induce the development of local vascular lesions [97]. Studies have shown that platelet aggregation is significantly enhanced and is in a hyperactive state in patients with DM, with consequent increase in microcapillary embolization and accelerated local vascular lesions [98, 99]. Increased platelet activities, such as altered morphology and function, may play a vital role in the development of diabetic vascular complications [100]. A study found that increased levels of the mean platelet volume, plateletcrit (PCT), and platelet-large cell ratio (P-LCR) are positively associated with the occurrence of increased HbA1c, retinopathy, nephropathy, and neuropathy individually in patients with DM [101]. Chronic hyperglycemia has been established as the cause of platelet activation and platelet hyperactivity in patients with DM [102]. For example, the profound increase in urinary excretion of 11-dehydro-TXB2 in patients with T2D suggests that acute hyperglycemia induces increased platelet activation from high shear-stress conditions [103]. T2D is associated with a greater production of 8-iso-PGF2α, a stable compound of non-cyclooxygenase peroxidation of arachidonic acid inducing vasoconstriction and platelet activation [104]. Basili et al. [105] found that acute glucose fluctuations strongly correlated with urinary excretion of 8-iso-PGF2α, but no relationship was observed when urinary 8-iso-PGF2α excretion rates were plotted against main markers of sustained hyperglycemia (HbA1c and mean daily glucose concentrations). In our previous study, we explored platelet aggregation in HUVECs exposed to different GV media and healthy platelets and found that endothelial cells intermittently incubated with high glucose showed a more relevant increase in maximum platelet aggregation rate than the increase observed in the stable high-glucose condition [106].

The significant factors causing increased platelet reactivity in patients with DM are hyperglycemia and insulin resistance. Hyperglycemia can cause dysfunctional platelet adhesion, aggregation, and release through the following mechanisms (▶ **Fig. 2**) [107, 108]. First, hyperglycemia is responsible for non-enzymatic glycation of proteins on the surface of the platelet, which decreases membrane fluidity and increases the propensity of platelets to become activated [109]. Next, the platelet activation signalling pathway is ultimately mediated by glycoprotein IIb/IIIa receptor (GPIIb/IIIa) platelet-fibrin interaction. Hyperglycemia leads to the release of larger platelets with more GPIb and GPIIb/IIIa receptors, thus increasing the aggregation baseline activation and thromboxane-forming capacity [110]. Third, both acute and chronic hyperglycemia induce increased protein kinase C (PKC) *in vivo*, a transduction pathway that triggers platelet activation [111]. Fourth, hyperglycemia promotes increased non-enzymatic glycation of circulating low-density lipoprotein, which may cause platelet dysfunction by increasing intracellular calcium concentration and platelet NO production [112, 113]. As an important second messenger, calcium participates in the regulation of a series of platelet functions, including morphological changes, secretion, aggregation, and thromboxane synthesis. Lastly, hyperglycemia induces the coagulation mechanism by increasing the release of prothrombotic molecules (e. g., tissue factor and von Willebrand factor [vWF]) while inhibiting fibrinolysis by increasing plasminogen activator inhibitor-1 (PAL-1) concentration [114, 115]. A high level of vWF in the circulation correlates with increased platelet activation, suggesting that acute, short-term hyperglycemia in T2D may precipitate vascular occlusions by facilitating platelet activation [116]. Additionally, mechanisms of platelet dysfunction in DM include upregulation of platelet P2Y purinoceptor 12 signalling, increased generation of thrombin, increased production of thromboxane A2 from arachidonic acid metabolism, and accelerated platelet turnover [117].



▶ **Fig. 2** Schematic representation of the main processes involved in the pathogenesis of platelet hyperactivation in patients with diabetes with glycemia variability (GV). PKC: Protein kinase C; GP: Glycoprotein.

Nowadays, several studies have demonstrated that some antidiabetic agents also have antithrombotic effects. The potential benefit to platelets may be related to the normalization of glycemic control, but other additional direct antithrombotic and anti-inflammatory mechanisms may be involved. The modulation of platelet activation by antidiabetic drugs may mitigate the risk of thrombotic events and contribute to cardiovascular protection in patients with DM [118]. Metformin, recommended as first-line therapy for newly diagnosed T2D by the American Diabetes Association, is associated with decreased cardiovascular risk, such as significant reduction in cardiovascular endpoints (MI and stroke) or all-cause mortality [119] and decreased macrovascular complications (MI, stroke, peripheral vascular disease) in patients with DM already on insulin therapy [120].

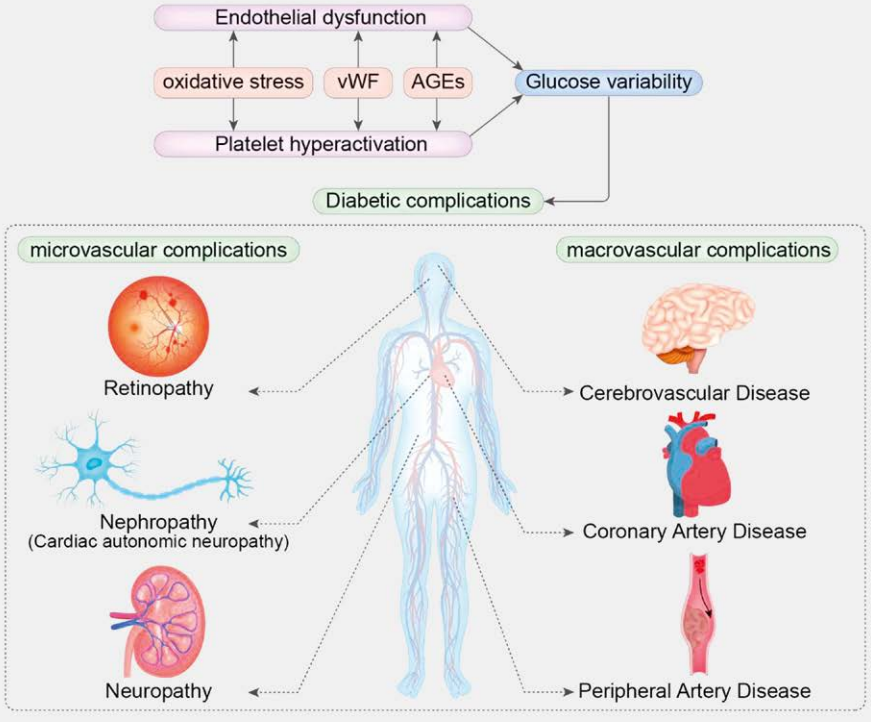
Interaction between endothelial dysfunction and platelet hyperactivation in vascular complications of DM

Several studies have demonstrated that hyperglycemia is the main mediator of endothelial dysfunction and platelet hyperaggregation in DM, which contributes to the development and progression of vascular complications. Interestingly, both endothelial dysfunction and platelet hyperactivation also regulate hyperglycemia-induced diabetic complications (▶ **Fig. 3**). However, their influence on this process remains unclear and needs further investigation.

Oxidative stress is the first link in the interaction between endothelial dysfunction and platelet hyperactivation in vascular complications of DM. Superoxide may increase platelet reactivity by enhancing intraplatelet activity to release calcium after activation [121]. In addition, oxidative stress impairs endothelial function and reduces the production of NO, thus increasing platelet reactivity [122].

The second link of the interaction is vWF, which is a glycoprotein released into the circulation by secretion from endothelial cells. Studies have reported that an elevated level of vWF is associated with a higher risk of thrombotic cardiovascular events in patients with DM [123, 124]. Hu et al. [125] showed that hyperglycemia-induced repression of microRNA-24 increases vWF expression and secretion in both patients with DM and diabetic mouse models. When the endothelial layer is disrupted, vWF binds to exposed collagen and then anchors platelets to the subendothelium. In addition, vWF is also able to bind to GPIb-IX and IIb-IIIa platelet receptors, promoting platelet aggregation and causing platelet plug formation [126].

Advanced glycation end-products (AGEs) mediate the linkage between endothelial dysfunction and platelet hyperactivation. Previous data have indicated that increased AGE production under hyperglycemic conditions can induce decreased endothelial NOS expression and increased endothelin-1 expression and ROS through AGE-specific receptors, leading to endothelial dysfunction [127, 128]. This further results in impaired vasodilatory response to NO [129] and enhancement of platelet aggregation *in vivo* and *in vitro*[130]. Another mechanism linking AGEs and platelet hyperreactivity is the increased expression of CD36, CD62, and CD63 on the platelet sur-



▶ **Fig. 3** Schematic representation of the interaction between endothelial dysfunction and platelet hyperactivation in diabetic vascular complications with glycemia variability (GV). vWF: von Willebrand factor; AGE: Advanced glycation end-product.

face membrane [131, 132], which is associated with enhanced platelet reactivity *in vitro* as well as enhanced arterial thrombosis *in vivo*.

Conclusions

The long-term hyperglycemic state in patients with DM leads to the development and progression of microvascular and macrovascular complications of DM and increases their all-cause and cardiovascular mortality. Current research shows that GV leads to the development of vascular complications in patients with DM. Therefore, aside from FPG, postprandial blood glucose, and HbA1c, glycemic fluctuations should also be considered when formulating a blood glucose-lowering regimen. In addition, GV should be a target of clinical intervention. GV measurement has become more accurate with the development of new technologies (e. g., CGM systems) and provides directions for clinical and basic research. However, there is still no gold standard for measuring GV. Further, more studies on the effects of glycemic fluctuations on vascular complications in patients with DM should be conducted, with the reduction of glycemic fluctuations as a therapeutic target. This will help clarify the effect of GV on hard endpoints such as the development and progression of microvascular and cardiovascular events in patients. An increasing number of clinical and basic studies are investigating the molecular mechanism of vascular complications mediated by GV. It appears that endothelial dysfunction and platelet hyperactivation mediated by excessive oxidative stress play important roles, and in-depth research on molecular mechanisms related to GV is needed to obtain data for developing novel treatment regimens. Due to two mechanisms of blood glucose fluctuations mediating diabetes complications in our paper, the literature cited were mainly basic studies. So clinical studies were not mentioned, which was our limitation. However, our previous study focused on the relationship between blood glucose fluctuation and the prognosis of diseases, especially in critically ill patients [133]. The correlation between GV and macro- or micro-vascular complications of T1D or T2D as well as other critical diseases remains to be further explored.

Author Contributions

Conceptualization and funding acquisition: YH and JW; Writing of the original draft: YH and LY; Writing, review, and editing: JQ, MG, JW; Supervision: SL. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Tuomilehto J, Lindstrom J, Eriksson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344: 1343–1350

[2] Dal Canto E, Ceriello A, Rydén L et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol 2019; 26: 25–32

[3] Zaccardi F, Pitocco D, Ghirlanda G. Glycemic risk factors of diabetic vascular complications: the role of glycemic variability. Diabetes Metab Res Rev 2009; 25: 199–207

[4] Muggeo M, Verlato G, Bonora E et al. Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients: the Verona Diabetes Study. Diabetologia 1995; 38: 672–679

[5] Muggeo M, Verlato G, Bonora E et al. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: the Verona Diabetes Study. Circulation 1997; 96: 1750–1754

[6] Zhou JJ, Koska J, Bahn G et al. Glycaemic variation is a predictor of all-cause mortality in the Veteran Affairs Diabetes Trial. Diab Vasc Dis Res 2019; 16: 178–185

[7] Nordwall M, Arnqvist HJ, Bojestig M et al. Good glycemic control remains crucial in prevention of late diabetic complications-the Linkoeping Diabetes Complications Study. Pediatr Diabetes 2009; 10: 168–176

[8] Sakamoto M. Type 2 Diabetes and glycemic variability: various parameters in clinical practice. J Clin Med Res 2018; 10: 737–742

[9] Monnier L, Colette C, Boegner C et al. Continuous glucose monitoring in patients with type 2 diabetes: Why? When? Whom? Diabetes Metab 2007; 33: 247–252

[10] Lachin JM, Bebu I, Bergenstal RM et al. Association of glycemic variability in type 1 diabetes with progression of microvascular outcomes in the diabetes control and complications trial. Diabetes Care 2017; 40: 777–783

[11] Zhou JJ, Schwenke DC, Bahn G et al. Glycemic variation and cardiovascular risk in the Veterans Affairs Diabetes Trial. Diabetes Care 2018; 41: 2187–2194

[12] Ceriello A, Kilpatrick ES. Glycemic variability: both sides of the story. Diabetes Care 2013; 36: S272–S275

[13] Picard F, Adjedj J, Varenne O. Diabetes mellitus, a prothrombotic disease. Ann Cardiol Angeiol 2017; 66: 385–392

[14] Tylee TS, Trence DL. Glycemic variability: looking beyond the A1C. Diabetes. Spectrum 2012; 25: 149–153

[15] Pandit K. Continuous glucose concentration monitoring. Indian J Endocrinol Metab 2012; 16: S263–S266

[16] Monnier L, Colette C. Glycemic variability: should we and can we prevent it? Diabetes Care 2008; 31: S150–S154

[17] Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405–412

[18] Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003; 26: 881–885

[19] Cameron FJ, Donath SM, Baghurst PA. Measuring glycaemic variation. Curr Diabetes Rev 2010; 6: 17–26

[20] Service FJ, Molnar GD, Rosevear JW et al. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970; 19: 644–655

[21] Kohnert KD, Heinke P, Vogt L et al. Utility of different glycemic control metrics for optimizing management of diabetes. World J Diabetes 2015; 6: 17–29

[22] Hill HR, Hindmarsh PC, Stevens RJ et al. A method for assessing quality of control from glucose profiles. Diabet Med 2007; 24: 753–758

[23] Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol Therap 2009; 11: S55–S67

[24] Shima K, Tanaka R, Morishita S et al. Studies on the etiology of "brittle diabetes". Relationship between diabetic instability and insulinogenic reserve. Diabetes 1977; 26: 717–725

[25] Guillermo EU, Boris PK. Glycemic variability: how to measure and its clinical implication for type 2 diabetes. Am J Med Sci 2018; 356: 518–527

[26] Bergenstal RM. Glycemic variability and diabetes complications: does it matter? simply put, there are better glycemic markers!. Diabetes Care 2015; 38: 1615–1621

[27] Muggeo M, Zoppini G, Bonora E et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: The Verona Diabetes Study. Diabetes Care 2000; 23: 45–50

[28] Bragd J, Adamson U, Backlund LB et al. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? Diabetes Metab 2008; 34: 612–616

[29] Kovatchev BP, Cox DJ, Gonder-Frederick LA et al. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care 1998; 21: 1870–1875

[30] Kovatchev BP. Metrics for glycaemic control–from HbA1c to continuous glucose monitoring. Nat Rev Endocrinol 2017; 13: 425–436

[31] Alemzadeh R, Loppnow C, Parton E et al. Glucose sensor evaluation of glycemic instability in pediatric type 1 diabetes mellitus. Diabetes Technol Ther 2003; 5: 167–173

[32] Kovatchev BP, Otto E, Cox D et al. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006; 29: 2433–2438

[33] Service FJ, Nelson RL. Characteristics of glycemic stability. Diabetes Care 1980; 3: 58–62

[34] Ryan EA, Shandro T, Green K et al. Assessment of the severity of hypoglycemia and glycemic lambility in type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004; 53: 955–962

[35] Nusca A, Pantano AL, Melfi 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; 250201

[36] Metzger M, Leibovitz G, Wainstein J et al. Reproducibility of glucose measurements using the glucose sensor. Diabetes Care 2002; 25: 1185–1191

[37] Danne T, Nimri R, Battelino T et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017; 40: 1631–1640

[38] Battelino T, Danne T, Bergenstal RM et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019; 42: 1593–1603

[39] Kilpatrick ES. Arguments for and against the role of glucose variability in the development of diabetes complications. J. Diabetes Sci Technol 2009; 3: 649–655

[40] Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. Diabetes Obes Metab 2010; 12: 288–298

[41] Caprnda M, Mesarosova D, Ortega PF et al. Glycemic variability and vascular complications in patients with type 2 diabetes mellitus. Folia Medica 2017; 59: 270–278

[42] Paneni F, Costantino S, Cosentino F. Molecular mechanisms of vascular dysfunction and cardiovascular biomarkers in type 2 diabetes. Cardiovasc Diagn Ther 2014; 4: 324–332

[43] Jung HS. Clinical implications of glucose variability: chronic complications of diabetes. Endorinol Metab 2015; 30: 167–174

[44] Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabetes Obes Metab 2013; 15: 3–8

[45] Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008; 26: 77–82

[46] Ceriello A, Kilpatrick ES. Glycemic variability: both sides of the story. Diabetes Care 2013; 36: S272–S275

[47] Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. Diabetes Obes Metab 2010; 12: 288–298

[48] Cardoso CRL, Leite NC, Moram CBM et al. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. Cardiovasc Diabetol 2018; 17: 33

[49] Lachin JM, Genuth S, Nathan DM et al. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and exposure on the risk of microvascular complications in the diabetes control and complications trial-revisited. Diabetes 2008; 57: 995–1001

[50] Smith-Palmer J, Brandle M, Trevisan R et al. Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. Diabetes Res Clin Pract 2014; 105: 273–284

[51] DCCT Research Group The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44: 968–983

[52] Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010; 376: 124–136

[53] Hsu CR, Chen TY, Sheu WHH. Glycemic variability and diabetes retinopathy: a missing link. J Diabetes Complicat 2015; 29: 302–306

[54] Schreur V, van Asten F, Ng H et al. Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. Acta Ophthalmol 2018; 96: 459–464

[55] Yang YF, Li TC, Li CI et al. Visit-to-visit glucose variability predicts the development of end-stage renal disease in type 2 diabetes: 10-year follow-up of Taiwan diabetes study. Medicine 2015; 94: e1804

[56] Kwai NCG, Arnold R, Poynten AM et al. Association between glycemic variability and peripheral nerve dysfunction in type 1 diabetes. Muscle Nerve 2016; 54: 967–969

[57] Nyiraty S, Pesei F, Orosz A et al. Cardiovascular autonomic neuropathy and glucose variability in patients with Type 1 diabetes: is there an association? Front Endocrinol 2018; 9: 174

[58] Matsutani D, Sakamoto M, Iuchi H et al. Glycemic variability in continuous glucose monitoring is inversely associated with baroreflex sensitivity in type 2 diabetes: a preliminary report. Cardiovasc Diabetol 2018; 17: 36

[59] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019; 7: 221–230

[60] Yang CP, Li CI, Lin WY et al. Variability of fasting plasma glucose increased risks of diabetic polyneuropathy in T2DM. Neurology 2017; 88: 944–951

[61] Anand SS, Islam S, Rosengren A et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008; 29: 932–940

[62] Zhang X, Xu X, Jiao X et al. The effects of glucose fluctuation on the severity of coronary artery disease in type 2 diabetes mellitus. J. Diabetes Res 2013; 2013: 576916

[63] Beliaeva N, Strongin L, Baranov E. The impact of glycemic variability on local contractility of the left ventricular in acute period of myocardial infarction. Cardiology 2013; 126: 93

[64] Gerbaud E, Darier R, Montaudon M et al. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. Diabetes Care 2019; 42: 674–681

[65] Takahashi H, Iwahashi N, Kirigaya J et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. Cardiovasc Diabetol 2018; 17: 116

[66] Francesco M, Lorenzo C, Domenico C. Glycaemic control and vascular complications in diabetes mellitus type 2. Adv Exp Med Biol 2021; 1307: 129–152

[67] Huang J, Zhang X, Li J et al. Impact of glucose fluctuation on acute cerebral infarction in type 2 diabetes. Can J Neurol Sci 2014; 41: 486–492

[68] Wattankit K, Folsom AR, Selvin E et al. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis 2005; 180: 389–397

[69] Yang CP, Lin CC, Li CL et al. Fasting plasma glucose variability and HbA1c are associated with peripheral artery disease risk in type 2 diabetes. Cardiovasc Diabetol 2020; 19: 4

[70] Tabit CE, Chung WB, Hamburg NM et al. Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications. Rev Endocr Metab Disord 2010; 11: 61–74

[71] Carrizzo A, Lzzo C, Oliveti M et al. The main determinants of diabetes mellitus vascular complications: endothelial dysfunction and platelet hyperaggregation. Int J Mol Sci 2018; 19: 2968

[72] Shi Y, Vanhoutte PM. Macro- and microvascular endothelial dysfunction in diabetes. J Diabetes 2017; 9: 434–449

[73] Jung HS. Clinical implications of glucose variability: chronic complications of diabetes. Endocrinol Metab 2015; 30: 167–174

[74] Cerielo A, Taboga C, Tonutti L et al. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation. Circulation 2002; 106: 1211–1218

[75] Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol 2019; 11: 45–63

[76] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005; 54: 1615–1625

[77] Monnier L, Mas E, Ginet C et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006; 295: 1681–1687

[78] Wang J-S, Huang Y, Zhang S et al. A protective role of paeoniflorin in fluctuant hyperglycemia induced vascular endothelial injuries through anti-oxidative and anti-inflammatory effects and reduction of PKCβ1. Oxid Med Cell Longev 2019; 5647219:

[79] Risso A, Mercuri F, Quagliaro L et al. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am J Physiol Endocrinol Metab 2001; 281: E924–E930

[80] Quagliaro L, Piconi L, Assaloni R et al. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes 2003; 52: 2795–2804

[81] Moncada S, Higgs EA. The discovery of nitric oxide and its role in vascular biology. Br J Pharmacol 2006; 147: S193–S201

[82] Forte M, Conti V, Damato A et al. Targeting nitric oxide with natural derived compounds as a therapeutic strategy in vascular diseases. Oxid Med Cell Longev 2016; 7364138

[83] Tousoulis D, Kampoli AM, Stefanadis C. Diabetes mellitus and vascular endothelial dysfunction: current perspectives. Curr Vasc Pharmacol 2011; 10: 19–32

[84] Puca AA, Carrizzo A, Ferrario A et al. Endothelial nitric oxide synthase, vascular integrity and human exceptional longevity. Immun Ageing 2012; 9: 26

[85] Harrison DG. Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Investig 1997; 100: 2153–2157

[86] Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr 2019; 13: 1165–1172

[87] Otsuka A, Azuma K, Iesaki T et al. Temporary hyperglycaemia provokes monocyte adhesion to endothelial cells in rat thoracic aorta. Diabetologia 2005; 48: 2667–2674

[88] Watada H, Azuma K, Kawamori R. Glucose fluctuation on the progression of diabetic macroangiopathy-new findings from monocyte adhesion to endothelial cells. Diabetes Res Clin Pract 2007; 77: S58–S61

[89] Mita T, Otsuka A, Azuma K et al. Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E-deficient mice. Biochem Biophys Res Commun 2008; 358: 679–685

[90] Piconi L, Quagliaro L, Da Ros R et al. Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly(ADP-ribose) polymerase. J Thromb Haemost 2004; 2: 1453–1459

[91] Quagliaro L, Piconi L, Assaloni R et al. Intermittent high glucose enhances ICAM-1, VCAM-1 and E-selectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production. Atherosclerosis 2005; 183: 259–267

[92] Liu T, Gong J, Chen Y et al. Periodic vs constant high glucose in inducing pro-inflammatory cytokine expression in human coronary artery endothelial cells. Inflamm Res 2013; 62: 697–701

[93] Esposito K, Nappo F, Marfella R et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002; 106: 2067–2072

[94] Shanmugam N, Reddy MA, Guha M et al. High glucose-induced expression of proinflammatory cytokine and chemokine genes in monocytic cells. Diabetes 2003; 52: 1256–1264

[95] Wu N, Shen HT, Liu HN 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

[96] Buch A, Kaur S, Nair R et al. Platelet volume indices as predictive biomarkers for diabetic complications in type 2 diabetic patients. J Lab Physicians 2017; 9: 84–88

[97] Gaiz A, Mosawy S, Colson N et al. Thrombotic and cardiovascular risks in type two diabetes; Role of platelet hyperactivity. Biomed Pharmacother 2017; 94: 679–686

[98] Rollini F, Franchi F, Muñiz-Lozano A et al. Platelet function profiles in patients with diabetes mellitus. J Cardiovasc Transl Res 2013; 6: 329–345

[99] Ang L, Palakodeti V, Khalid A et al. Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. J Am Coll Cardiol 2009; 52: 1052–1059

[100] Kodiatte TA, Manikyam UK, Rao SB et al. Mean platelet volume in Type 2 diabetes mellitus. J Lab Physicians 2012; 4: 5–9

[101] Walinjkar RS, Khadse S, Kumar S et al. Platelet indices as a predictor of microvascular complications in type 2 diabetes. Indian J Endocrinol Metab 2019; 23: 206–210

[102] Davì G, Catalano I, Averna M et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. N Engl J Med 1990; 322: 1769–1774

[103] Gresele P, Guglielmini G, De Angelis M et al. Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. J Am Coll Cardiol 2003; 41: 1013–1020

[104] Davi G, Alessandrini P, Mezzetti A et al. In vivo formation of 8-Iso-Prostaglandin F-2 alpha is increased in hypercholesterolemia. An aspirin-insensitive amplification mechanism of platelet activation. Thromb Res 1998; 91: S131

[105] Basili S, Pacini G, Guagnano MT et al. Insulin resistance as a determinant of platelet activation in obese women. J Am Coll Cardiol 2008; 48: 2531–2538

[106] Huang Y, Wang J-S, Yang L et al. Paeoniflorin ameliorates glycemic variability-induced oxidative stress and platelet activation in HUVECs and DM rats. RSC Adv 2020; 10: 42605–42612

[107] Linden MD, Tran H, Woods R et al. High platelet reactivity and antiplatelet therapy resistance. Semin Thromb Hemost 2012; 38: 200–212

[108] Tang WH, Stitham J, Gleim S et al. Glucose and collagen regulate human platelet activity through aldose reductase induction of thromboxane. J Clin Invest 2011; 121: 4462–4476

[109] Vinik AI, Erbas T, Park TS et al. Platelet dysfunction in type 2 diabetes. Diabetes Care 2001; 24: 1476–1485

[110] Tschoepe D. The activated megakaryocyte-platelet-system in vascular disease: focus on diabetes. Semin Thromb Hemost 1995; 21: 152–160

[111] Assert R, Scherk G, Bumbure A et al. Regulation of protein kinase C by short term hyperglycaemia in human platelets in vivo and in vitro. Diabetologia 2001; 44: 188–195

[112] Millican SA, Schultz D, Bagga M et al. Glucose-modified low density lipoprotein enhances human monocyte chemotaxis. Free Rad Res 1998; 28: 533–542

[113] Ferretti G, Rabini RA, Bacchetti T et al. Glycated low density lipoproteins modify platelet properties: a compositional and functional study. J Clin Endocrinol Metab 2002; 87: 2180–2184

[114] Boden G, Rao AK. Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. Curr Diab Rep 2007; 7: 223–227

[115] Kessler L, Wiesel ML, Attali P et al. Von Willebrand factor in diabetic angiopathy. Diabetes Metab 1998; 24: 327–336

[116] Gresele P, Guglielmini G, De Angelis M et al. Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. J Am Coll Cardiol 2003; 41: 1013–1020

[117] Patti G, Cavallari I, Andreotti F et al. Prevention of atherothrombotic events in patients with diabetes mellitus: from antithrombotic therapies to new-generation glucose-lowering drugs. Nat Rev Cardiol 2019; 16: 113–130

[118] Nusca A, Tuccinardi D, Pieralice S et al. Platelet effects of anti-diabetic therapies: new perspectives in the management of patients with diabetes and cardiovascular disease. Front Pharmacol 2021; 12: 670155

[119] King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol 1999; 48: 643–648

[120] Lehert P, Bets D, Donker AJ et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009; 169: 616–625

[121] Schaeffer G, Wascher TC, Kostner GM et al. Alterations in platelet Ca^{2+} signalling in diabetic patients is due to increased formation of superoxide anions and reduced nitric oxide production. Diabetologia 1999; 42: 167–176

[122] Spinetti G, Kraenkel N, Emanueli C et al. Diabetes and vessel wall remodelling: from mechanistic insights to regenerative therapies. Cardiovasc Res 2008; 78: 265–273

[123] Frankel DS, Meigs JB, Massaro JM et al. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: The framingham offspring study. J Vasc Surg 2009; 50: 235

[124] van Schie MC, de Maat MP, Isaacs A et al. Variation in the von Willebrand factor gene is associated with von Willebrand factor levels and with the risk for cardiovascular disease. Blood 2011; 117: 1393–1399

[125] Xiang Y, Cheng J, Wang D et al. Hyperglycemia repression of miR-24 coordinately upregulates endothelial cell expression and secretion of von Willebrand factor. Blood 2015; 125: 3377–3387

[126] Etheresia P. Platelets as potent signaling entities in type 2 diabetes mellitus. Trends Endocrinol Metab 2019; 30: 532–545

[127] Quehenberger P, Bierhaus A, Fasching P et al. Endothelin 1 transcription is controlled by nuclear factor-kappaB in AGE-stimulated cultured endothelial cells. Diabetes 2000; 49: 1561–1570

[128] Xu B, Chibber R, Ruggiero D et al. Impairment of vascular endothelial nitric oxide synthase activity by advanced glycation end products. FASEB J 2003; 17: 1289–1291

[129] Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. J Clin Invest 1991; 87: 432–438

[130] Hangaishi M, Taguchi J, Miyata T et al. Increased aggregation of human platelets produced by advanced glycation end products in vitro. Biochem. Biophys Res Commun 1998; 248: 285–292

[131] Gawlowski T, Stratmann B, Ruetter R et al. Advanced glycation end products strongly activate platelets. Eur J Nutr 2009; 48: 475–481

[132] Zhu W, Li W, Silverstein RL. Advanced glycation end products induce a prothrombotic phenotype in mice via interaction with platelet CD36. Blood 2012; 119: 6136–6144

[133] Zhang X, Zhang J, Li J et al. Relationship between 24h venous blood glucose variation and mortality among patients with acute respiratory failure. Sci Rep 2021; 11: 7747