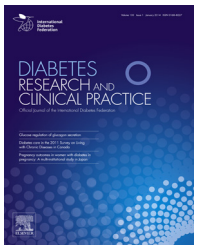
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Review

Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes☆

J. Smith-Palmer[a,*], M. Brändle[b], R. Trevisan[c], M. Orsini Federici[d], S. Liabat[e], W. Valentine[a]

[a] Ossian Health Economics and Communications, Basel, Switzerland
[b] Kantonsspital St. Gallen, St. Gallen, Switzerland
[c] Ospedali Riuniti di Bergamo, Bergamo, Italy
[d] Medtronic Italia, S.p.A, Milano, Italy
[e] Medtronic International Trading Sàrl, Tolochenaz, Switzerland

ARTICLE INFO

Article history:
Received 16 January 2014
Received in revised form
28 April 2014
Accepted 15 June 2014
Available online 23 June 2014

Keywords:
Glycemic variability
Microvascular complications
Macrovascular complications

ABSTRACT

Chronic hyperglycemia is the main risk factor for the development of diabetes-related complications in both type 1 and type 2 diabetes, but it is thought that frequent or large glucose fluctuations may contribute independently to diabetes-related complications.

A systematic literature review was performed using the PubMed, EMBASE and Cochrane Library databases with searches limited to studies published from June 2002 to March 2014, in English and including ≥50 patients. Twenty eight articles were included in the final review.

Eighteen studies reported the association between glucose variability and diabetes-related complications exclusively in type 2 diabetes. A positive association between increased variability and microvascular complications and coronary artery disease was consistently reported. Associations between glucose variability and other macrovascular complications were inconsistent in type 2 diabetes.

Seven studies examined the association between glucose variability and complications exclusively in type 1 diabetes. Increased glucose variability appears to play a minimal role in the development of micro- and macrovascular complications in type 1 diabetes.

Consistent findings suggest that in type 2 diabetes glucose variability is associated with development of microvascular complications. The role of increased glucose variability in terms of microvascular and macrovascular complications in type 1 diabetes is less clear; more data in are needed.

☆ This study was supported by funding from Medtronic International Trading Sàrl.
* *Corresponding author at*: Ossian Health Economics and Communications, GmbH, Bäumleingasse 20, 4051 Basel, Switzerland. Tel.: +41 61 271 6214.
E-mail address: smith-palmer@ossianconsulting.com (J. Smith-Palmer).
http://dx.doi.org/10.1016/j.diabres.2014.06.007
0168-8227/

Contents

1. Introduction

Diabetes guidelines state that optimal glycemic control, defined by glycated hemoglobin (HbA1c), is a fundamental treatment goal [1]. A wealth of studies, in type 1 and type 2 diabetes, including the landmark Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have shown that chronic hyperglycemia is the main risk factor for the development of diabetes-related complications. However, a key caveat of HbA1c is that it does not capture information relating to short-term fluctuations in glucose levels, which have been postulated to have an independent role in the etiology of diabetes-related complications [2]. The development of continuous glucose monitoring (CGM) systems has paved the way for accurate measurement of short-term glucose variability and the investigation of the role of glucose fluctuations in the development of diabetes-related complications [3,4]. A number of early studies used 7- or 8-point self-monitoring of blood glucose (SMBG) profiles to assess glucose variability; however, a disadvantage of this was that SMBG-based studies typically yield little information on nocturnal glycemic patterns.

Glycemic fluctuations are manifest principally as post-prandial glycemic spikes and minor (or asymptomatic) hypoglycemia. However, the term glycemic variability may refer to within day variability, variability between daily means, or within series variability. Several methods have been proposed for the measurement of glucose variability including standard deviation or coefficient of variation, the mean amplitude of glycemic excursions (MAGE) for intra-day variability, the mean of daily differences (MODD) for inter-day variability, high blood glucose index (HBGI), low blood glucose index (LBGI), glycemic risk assessment diabetes equation (GRADE), or continuous overlapping net glycemic action (CONGA) (more details on the methodology for each of the methods mentioned are provided in a 2013 review by Service) [5]. However, at present there is little consensus regarding which method offers the most meaningful assessment of glucose variability.

It has also been suggested that indicators of variability may provide a better indication than HbA1c of overall long-term problems with glycemic control [6]. In short-term (<1 month), retrospective, general population studies of critically ill patients, glucose variability has been implicated in increased mortality rates, as such there is increasing interest in the possible role of glucose variability in the development and underlying pathology of diabetes-related complications [7,8]. In vitro studies have shown that glucose fluctuations are linked to pathologic processes including the production of reactive oxygen species with some studies suggesting that large fluctuations in glucose levels may be a greater trigger of oxidative stress processes than chronic sustained levels of hyperglycemia [9].

To more fully elucidate the role of short-term glucose variability in the development of long-term complications in type 1 and type 2 diabetes, a systematic literature review was performed. The aim of the current review was to establish whether the current evidence base suggests if, and the extent to which, short-term glucose variability is involved in the development of chronic diabetes-related complications.

2. Methods

A systematic literature review was performed to identify studies investigating the relationship between short-term glucose variability and the incidence/prevalence of chronic complications in type 1 or type 2 diabetes. Searches were performed using the PubMed, EMBASE and Cochrane library databases. The search strategy was designed based on high level Medical Subject Heading (MeSH) terms (full details are provided in Appendix A). The search strategy was designed to capture articles where the main focus was on the association between chronic complications of diabetes and short-term measures of glucose variability rather than acute complications such as hypoglycemic events and diabetic ketoacidosis. Studies that captured measures of short-term (typically intra- or inter-day) glucose variability (including, but not limited to, SD, MAGE, and CONGA) assessed using either SMBG or CGM were included in the review (studies focusing on long-term variability of HbA1c were excluded from the present review). The time horizon was initially limited to articles published in the last 10 years (2002–2012) but an update of searches was performed in 2014 to ensure that the most recent data were captured in the review. Literature searches identified published congress abstracts in addition to full publications, which were included in the present review. Where abstracts were identified supplementary hand searches of the congress websites were performed to attempt to identify the full poster/presentation where possible. In instances where only the abstract was available, data available in the abstract were used, but no conclusions were drawn beyond methods, results, and conclusions presented by the authors in the abstract.

Following exclusion of duplicates, a total of 1718 unique hits remained in the initial literature searches, the titles and

abstracts of which were then screened for relevance (Fig. 1). A further 2 studies were identified through hand searches of conference proceedings and searches of bibliographic sections of included studies. In the 2014 update, a further 6 publications were identified for inclusion. Therefore, a total of 28 articles described studies were included in the final review (7 in type 1 diabetes, 18 in type 2 diabetes, 1 in a mixed population including both type 1 and type 2 diabetes and 2 systematic reviews).

3. Results

Summary findings of the literature review are outlined below in two separate sections. The first section deals with studies investigating the role of short-term glucose variability, independently of HbA1c, in the development of chronic complications in type 1 diabetes. The second describes the role of glucose variability in the development of chronic complications in type 2 diabetes.

3.1. *Short-term glucose variability and complications in type 1 diabetes*

The literature review identified 7 studies that examined the relationship between glucose variability and the development of diabetes-related complications in type 1 diabetes (Table 1) and one article that included a mixed cohort of patients with type 1 and type 2 diabetes. Notably, a large proportion of the included studies ($n = 5$) utilized patient data from the DCCT and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study. Three studies examined the relationship between glucose variability and the development/progression of microvascular complications (retinopathy and/or nephropathy), all of which were based on DCCT/EDIC. In particular, one of the studies included in the present review by Lachin et al. was a reanalysis of an earlier study by the DCCT group from 1995 and therefore the 1995 study was not included here [10,11]. The 1995 analysis was interpreted by Brownlee and Hirsch [2] to suggest that factors other than HbA1c were involved in the development/progression of retinopathy, proposing a role for glycemic variability in the etiology of retinopathy. However, the reanalysis by Lachin et al. did not agree with earlier findings and reported that almost all of the risk for retinopathy was attributable to HbA1c. These findings were largely supported by other analyses of DCCT by Kilpatrick et al. [50,51]. A 2013 study by Sartore et al. [55] on retinopathy was conducted in a mixed population of type 1 and type 2 diabetes patients. Multivariate analysis across both type 1 and type 2 diabetes showed no significant relationship between any measure of glucose variability and diabetic retinopathy.

Two studies examined the relationship between glucose variability and macrovascular disease, although one study by Snell-Bergeon et al. [3] reported data on subclinical atherosclerosis, a surrogate endpoint for overt cardiovascular disease, rather than definitive cardiovascular endpoints. Using data from the ongoing Coronary Artery Calcification

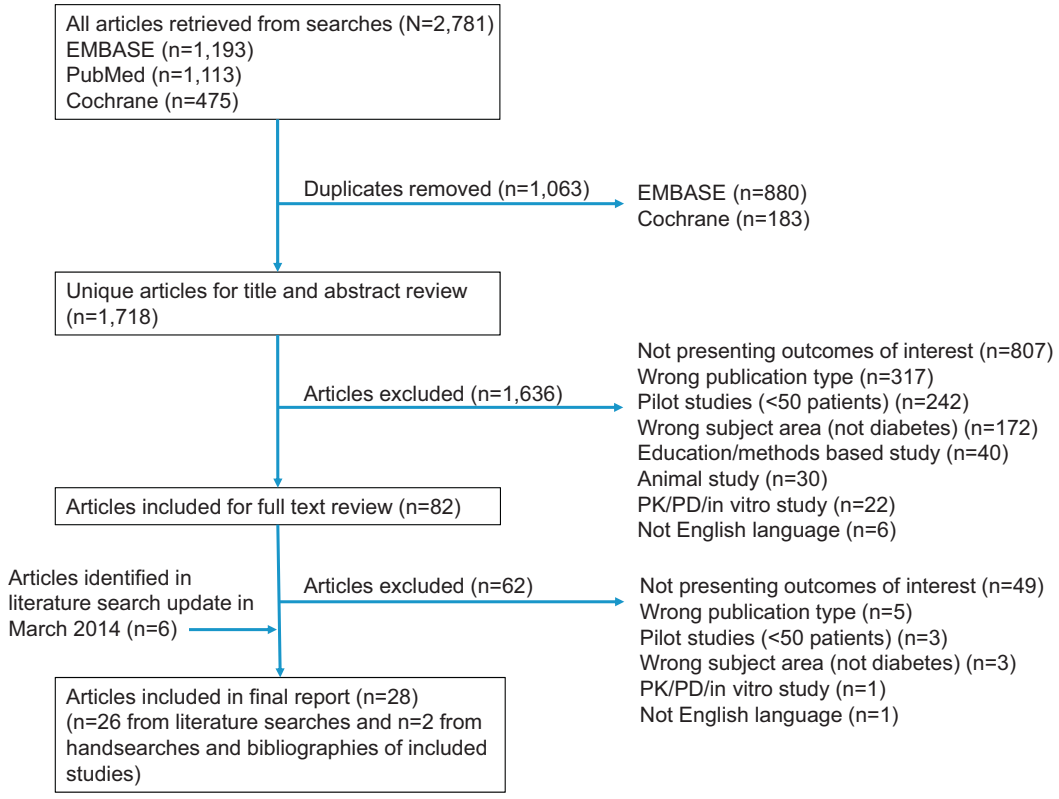


Fig. 1 – Flow diagram of literature review process.

Table 1 – Summary of studies investigating the association between short-term glucose variability and diabetes-related complication in patients with type 1 diabetes.

Study	Patients (*N*)	Study design	Method of blood glucose assessment	Measure of glucose variability	Endpoints	Key findings
Kilpatrick et al. [50]	1441	Post hoc analysis of data from the DCCT	7-Point SMBG	SD of daily blood glucose, SD of mean blood glucose (mean blood glucose calculated as area under the curve of 7-point plasma glucose [calculated using the trapezoidal rule]) at each quarter, mean pre-prandial glucose, mean post-prandial glucose	Diabetic retinopathy, diabetic nephropathy	Significant link between MBG (area under the curve) and retinopathy ($p < 0.0001$) but not with other measures of variability No association between nephropathy and any measure of variability
Kilpatrick et al. [51]	1208	Post hoc analysis of data from the DCCT/EDIC	7-Point SMBG	Mean blood glucose (calculated as area under the curve of 7-point SMBG profile), MAGE and SD of glycemic excursions	Diabetic retinopathy, diabetic nephropathy	Mean HbA1c was linked to the development of retinopathy and nephropathy ($p = 0.001$); no significant association between MAGE and retinopathy or nephropathy
Lachin et al. [11]	1441	Post hoc analysis of data from the DCCT	7-Point SMBG	Mean blood glucose	Diabetic retinopathy, diabetic nephropathy	Nearly all of the risk for development of retinopathy or nephropathy was attributable to HbA1c, only a small proportion of risk can be attributed to glycemic variability
Siegelaar et al. [52]	1160	Post hoc analysis of data from the DCCT	7-Point SMBG	Mean blood glucose (calculated as area under the curve of the 7-point plasma glucose profile), SD of mean daily blood glucose, MAGE	Neuropathy	No association between variability (SD of mean blood glucose; MAGE) and confirmed clinical neuropathy or nerve conduction abnormalities
Kilpatrick et al. [53]	1441	Post hoc analysis of data from the DCCT	7-Point SMBG	Within day SD of blood glucose, SD of blood glucose over time, AUC, mean pre- and post-prandial blood glucose	Macrovascular events (angina, fatal and non-fatal MI, coronary revascularization and major ECG events)	Significant association between mean blood glucose (area under the curve) and cardiovascular ($p = 0.019$) and all macrovascular risk ($p = 0.047$), but not for SD of mean blood glucose or HbA1c
Snell-Bergeon et al. [3]	75	Analysis of data from the Coronary Artery Calcification in Type 1 Diabetes Study; an ongoing cohort study	CGM	SD of all glucose values within 1 day, SD of average glucose for any time of day within days, SD of the mean glucose for each day (between day)	Subclinical atherosclerosis (assessed via coronary artery levels)	Significant independent relationship between increased glycemic variability and coronary artery calcification in men but not in women
Houssay et al. [54]	54	No study details provided	Method of blood glucose assessment not stated	Mean blood glucose, SD of mean glucose, HBGI, LBGI	Diabetic autonomic variability (assessed by heart rate variability)	Positive correlation between faster resting heart rate and greater amplitude of low frequency component of heart rate variability
Sartore et al. [55][a]	68	Prospective cross-sectional study	CGM	SD of the glucose rate of change, MAGE, CONGA-2	Diabetic retinopathy	On multivariate analysis (combining both type 1 and type 2 diabetes patients) there was no significant relationship between any measure of glucose variability and diabetic retinopathy

AUC, area under the curve; ESRD, end-stage renal disease; HBGI, high blood glucose index; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursion; MI, myocardial infarction; SD, standard deviation; SMBG, self-monitoring of blood glucose.

[a] Includes patients with type 1 diabetes and patients with type 2 diabetes.

in Type 1 Diabetes study ($N = 75$ patients) they noted that the relationship between glucose variability (within day and between day SD of mean blood glucose) and coronary artery calcium levels was gender-dependent, reporting a significant association between variability and increased coronary artery calcification in men but not in women. Furthermore, using DCCT data ($N = 1441$ patients) Kilpatrick et al. [53] reported that mean blood glucose was a better predictor of cardiovascular events than HbA1c, whereas measures of blood glucose variability, including the SD of mean blood glucose (within day), were not.

Overall, studies in type 1 diabetes in the present review did not show any association between short-term glucose variability and microvascular complications. With regard to the association between the development of macrovascular complications and glucose variability, the small number of studies identified does not allow any meaningful overall conclusions to be drawn. Further, prospective, long-term studies are needed to elucidate whether, and the extent to which, glucose variability is involved in the development of macrovascular complications in type 1 diabetes.

3.2. *Short-term glucose variability and complications in type 2 diabetes*

A total of 18 studies, of which 7 were post hoc or retrospective, were identified that investigated the association between parameters of short-term glucose variability and the incidence or progression of long-term complications in type 2 diabetes (Table 2). A total of six studies were conducted in patient populations that contained both patients treated with diet only, OADs or insulin [12,13,57,58,61,63]. Two studies were conducted exclusively in patients prescribed OADs only [14,59], two studies were conducted in insulin-treated patients [56,62] and treatment was not stated in eight studies [4,15–19,60,64].

The literature search identified six publications that investigated the role of glycemic variability in the development/progression of retinopathy (five were retrospective, and one did not provide details of study design). In an Italian-based retrospective analysis of data from a prospective observational study in 1019 patients Zoppini et al. [64] reported no significant relationship between the coefficient of variation of fasting plasma glucose (FPG) and the development/progression of diabetic retinopathy. In contrast, retrospective analyses by Takao et al. [58,63] ($N = 170$ patients) and Gimeno-Orna et al. [61] ($N = 130$ patients), which were conducted in populations containing both insulin-treated patients and those receiving OADs alone, reported that the SD of FPG and coefficient of variation were significant risk factors for the development/progression of retinopathy. These studies showed that FPG variability was a risk factor for retinopathy independently of HbA1c plasma levels. Furthermore, a cross-sectional study by Liu and He [15] showed that patients with retinopathy had significantly higher levels of MAGE and SD of mean blood glucose levels in comparison with patients without retinopathy, again suggesting glucose variability may be a predictor of microvascular complications.

Eight studies (two of which were retrospective or post hoc and six of which were prospective) investigated the role of glucose variability in the pathogenesis of cardiovascular complications. More specifically, two publications from prospective studies by the same group reported a significant association between higher levels MAGE and coronary artery disease (defined according to Gensini score) [4,57]. In a prospective study of 80 patients ($n = 50$ patients with type 2 diabetes and $n = 30$ age-matched controls) Yang et al. [17] also showed a positive association between glycemic variability (measured by SD of blood glucose, MAGE, MODD and area under the curve [AUC]) and diabetic cardiomyopathy. However, in contrast to the positive associations found by Yang et al. [56], an analysis of data from the HEART2D study reported no association between intra-day glucose variability and the endpoint of first combined cardiovascular event. Three articles (two from the same authors) [13,14,18] specifically looked at the relationship between short-term glucose variability measures including MAGE and subclinical atherosclerosis, measured by carotid intima–media thickness (IMT). All three publications reported a significant association between higher MAGE and subclinical atherosclerosis. Another study by Pochinka et al. [12] showed that in type 2 diabetes patients with heart failure MAGE above 5.0 mmol/L was significantly associated with dangerous ventricular arrhythmias.

The literature review also identified two large-scale studies ($N > 3000$ patients) examining the link between glycemic variability and mortality in type 2 diabetes. Both Klindukhova et al. [62] and Krinsley [60] reported no association between glycemic variability and mortality in patients in intensive care and post-operative mortality, respectively.

4. Discussion

It is well established that in both type 1 and type 2 diabetes, chronic hyperglycemia represents the main risk factor for the development of complications, although other risk factors including high blood pressure, dyslipidemia and the presence of proteinuria are also involved. Chronic hyperglycemia is almost universally assessed by HbA1c, which in a longitudinal study by Nathan et al. [20] has been shown to correlate closely with mean glucose levels over time, determined by CGM. The proportion of risk attributable to each risk factor may vary considerably depending on the complication and also on individual patient characteristics.

Moreover, the relative contribution of post-prandial glycemic excursions and fasting hyperglycemia to overall hyperglycemia has been the subject of considerable debate. Monnier et al. [21] suggested that the relative contribution of fasting and post-prandial glucose differ according to the level of overall glycemic control. They reported that the relative contribution of post-prandial glucose to overall glycemia decreases steadily and significantly from the lowest to highest HbA1c quintile. Similarly, the relative contribution of fasting glucose increases significantly with increasing HbA1c. Additionally, the relationship between glycemic variability and the time spent in a hyperglycemic state and beta-cell function has also been the subject of research efforts. Studies by Kohnert et al. [22,23] reported that on average patients were classed as being in the hyperglycemic range for 24% of the day and that

Table 2 – Summary of studies investigating the association between short-term glucose variability and diabetes-related complication in patients with type 2 diabetes.

Study	Patients (*N*)	Study design	Method of blood glucose assessment	Measure of glucose and variability	Endpoints	Key findings
Siegelaar et al. [56]	1115	Retrospective analysis of data from the HEART2D study; a randomized controlled trial of two insulin strategies	7-Point SMBG	Mean absolute glucose, MAGE, and SD of blood glucose	First combined cardiovascular event (composite of cardiovascular death, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome)	Lower intra-day glucose variability did not result in a reduction in cardiovascular outcomes
Su et al. [57]	344	Prospective observational study in consecutive patients with type 2 diabetes undergoing coronary angiography	CGM	MAGE, MODD, PPGE	Presence and severity of coronary artery disease (assessed via Gensini score)	MAGE and post-prandial glucose excursion were significantly higher in patients with CAD versus those without CAD, but no significant difference was reported for MODD. Gensini score was significantly correlated with MAGE ($r = 0.277$, $p < 0.001$) and PPGE ($r = 0.167$; $p = 0.002$) but not MODD
Mi et al. [4]	286	Prospective study in patients with newly diagnosed type 2 diabetes	CGM	MAGE	Coronary artery disease (severity assessed via Gensini score)	MAGE was significantly higher in patients with coronary artery disease versus those without ($p = 0.019$); high MAGE ($\geq$3.4 mmol/L) was an independent risk factor for coronary artery disease (and severity of CAD) in newly diagnosed diabetes patients (<0.001)
Liu and He [15]	80	Study design details not provided	CGM	SD of glucose levels, MAGE	Diabetic retinopathy	Patients with diabetic retinopathy had significantly higher MAGE ($p < 0.01$) and SD of glucose ($p < 0.01$)
Liu et al. [16]	59	Retrospective database analysis	CGM	Index of glucose variability not specified	Diabetic retinopathy and nephropathy	Significantly higher rates of retinopathy and nephropathy were reported in the high glycemic variability group versus the low variability group
Yang et al. [17]	*N* = 50 type 2 patients and *n* = 30 age matched controls	Prospective cohort study	CGM	SD of mean glucose, MAGE, largest amplitude of glycemic excursion, MODD	Diabetic cardiomyopathy	SD of glucose, MAGE; largest amplitude of glycemic excursion and MODD levels were significantly higher in patients with diabetic cardiomyopathy versus patients without diabetic cardiomyopathy
Takao et al. [58]	170	Retrospective chart review	Method of blood glucose assessment not stated	SD of FPG	Development and progression of diabetic retinopathy	High FPG SD was a significant risk factor for onset of mild-moderate non-proliferative diabetic retinopathy and for progression to severe non-proliferative diabetic retinopathy (independent of HbA1c or mean FPG)
Abbatecola et al. [59]	156	Randomized, open label controlled trial	Method of blood glucose assessment not stated	Coefficients of variation of PPG and FPG	Cognitive function (assessed by Mini Mental State Examination)	Significant correlation between coefficient of variation of FPG ($r = -0.2430$; $p < 0.001$) and CV-PPG ($r = -0.3410$; $p > 0.001$) and Mini Mental State Examination score
Krinsley [60]	4084	Retrospective chart analysis	Blood glucose measured every 1–3 h (method not stated)	Coefficient of variation of mean blood glucose level	Mortality	Significant association between glycemic variability and mortality in non-diabetes patients but not in patients with type 2 diabetes
Gimeno-Orna et al. [61]	130	Retrospective analysis of prospective cohort study data	Method of blood glucose assessment not stated	FPG coefficient of variation	Diabetic retinopathy	Coefficient of variation for FPG variability was a significant predictor for the onset of diabetic retinopathy ($p = 0.0013$)

Klindukhova et al. [62]	3184	Study design details not provided	Method of glucose assessment not stated	SD of post-operative blood glucose values	Mortality	Significant association between glycemic variability and mortality in non-diabetes subjects but no significant association in patients with diabetes
Takao et al. [63]	170	Retrospective chart review	Method of blood glucose assessment not stated	SD of FPG	Proliferative diabetic retinopathy	Significant association between FPG SD and development of proliferative diabetic retinopathy independent of HbA1c ($p < 0.0001$–0.0190 depending on model used)
Zoppini et al. [64]	1019	Retrospective analysis of data from a prospective observational study	Method of blood glucose assessment not stated	FPG coefficient of variation	Diabetic retinopathy	No significant relationship between FPG coefficient of variation and the development/progression of diabetic retinopathy
Mo et al. [13]	216	Prospective cross-sectional study	CGM	Intra-day SD of glucose and MAGE	Subclinical atherosclerosis measured by carotid IMT	In patients without stenosis both SD of glucose and MAGE were significantly associated with subclinical atherosclerosis
Mo et al. [18]	93	Study details not provided	GCM	SD of glucose and MAGE	Subclinical atherosclerosis measured by carotid IMT	In subjects without atherosclerotic lesions glucose variability was significantly associated with subclinical atherosclerosis
Zhong et al. [19]	248	Prospective cohort study	CGM	SD of glucose, difference between minimum and maximum glucose, MAGE and MODD	Cognitive function (mini-mental state examination, clinical dementia rating, global deterioration scale, and clock drawing test)	MAGE and SD of glucose were significantly negatively correlated with mini-mental state examination score
Pochinka et al. [12]	80	Study details not provided	CGM	MAGE	Ventricular arrhythmias (in patients with heart failure)	MAGE above 5.0 mmol/L was significantly associated with dangerous ventricular arrhythmias
Barbieri et al. [14]	90	Post hoc analysis of a prospective parallel group randomized controlled trial	Not stated	MAGE	Subclinical atherosclerosis measured by carotid IMT	At 3 months post DPP-IV inhibitor initiation changes in MAGE were significantly associated with changes in IMT (after adjustment for other cardiovascular risk factors)

FPG, fasting plasma glucose; IMT, intima–media thickness; MAGE, mean amplitude of glycemic excursion; PPG, post-prandial glucose; PPGE, post-prandial glucose excursion; SD, standard deviation; SMBG, self-monitoring of blood glucose.

the duration of hyperglycemia was closely correlated with both indices of chronic hyperglycemia and glycemic variability as well as a significant but non-linear correlation between MAGE and post-prandial and basal beta-cell function.

The central hypothesis for the underlying molecular mechanism behind the potential link between acute glucose fluctuations and the development of micro- and macrovascular complications is that of increased damage to vascular endothelial cells mediated by oxidative stress. The results of in vitro studies have shown that high levels of fluctuations in glucose levels lead to the production of reactive oxygen species. Downstream consequences of this include increased formation of advanced glycation endproducts and the activation of the nuclear factor κB and protein kinase C pathways, which ultimately lead to increased levels of vascular endothelial damage. Indeed, oxidative stress has been shown to be a key factor in the development of atherosclerosis and cardiovascular disease [24]. In addition, in type 2 diabetes increased oxidative stress has been correlated with increased levels of inflammation; there is some speculation that chronic low level inflammation may be a contributing factor in the development of long-term complications [9].

Overall, the findings of the present review largely agree with those earlier reviews [25,26] based on earlier evidence such as studies from the Verona Diabetes Study of type 2 diabetes, which report an association between increased variability in FPG and elevated risk of all-cause, cardiovascular and cancer-related mortality [27,28]. In contrast, there was a relative paucity of studies investigated mortality risk published from 2002 onwards. In total, four studies in type 1 diabetes [3,51,52,54] and sixteen studies in type 2 diabetes [4,12–19,56,57,58,60,62–64] were published since the November 2008 cut-off point of the earlier review by Nalysnyk et al. This suggests that even the most recent literature did not alter the previous conclusions. A point worthy of note with regard to type 1 diabetes is that the majority of glycemic variability studies identified in the current review were performed using data from the DCCT. In relation to this, Kilpatrick et al. [29] raise the point that the stringent inclusion/exclusion criteria applied to the DCCT were such that only around 20% of the total type 1 diabetes population would have been eligible for inclusion in the DCCT. Consequently, this may have implications in terms of the generalizability of findings based on DCCT data to the overall type 1 diabetes population.

In contrast to type 1 diabetes, findings from studies in type 2 diabetes support the possibility that increased levels of short-term glucose variability may have a substantial role in the development of microvascular complications. Less clear is the relationship between glucose variability and macrovascular complications and overall mortality. Two cross-sectional studies reported a positive association between short-term glucose variability and the presence of coronary artery disease (defined according to Gensini score) and three showed a significant association between increased MAGE and subclinical atherosclerosis, although findings with regard to other cardiovascular endpoints were inconsistent, which may be partly attributable to substantial heterogeneity between different patient populations.

As noted by Lin et al. [30] the inconsistency around the role of glucose fluctuations in the development of macrovascular disease raises the question of whether increased short-term glucose variability is a causative agent of diabetes-related complications or if increased glycemic fluctuations arise as a consequence of more severe disease and/or the presence of existing complications, poor dietary management or poor adherence to antidiabetic therapy. Another question that remains largely unanswered is the underlying causes of unpredictable glycemic fluctuations, and their relative contribution to long-term outcomes.

Another weakness in the studies in type 2 diabetes is that a substantial proportion of studies included mixed populations of patients treated with diet alone, diet and oral antidiabetic medications (OADs) and insulin. As such, this may have been a confounding factor in the findings of some analyses, with insulin treatment being indicative of more advanced disease, which is in turn associated with a higher risk for complications. Moreover, the degree of glycemic variability may differ between these sub-populations and sub-group analysis according to treatment would offer a valuable insight into the impact of OADs and insulin on glycemic variability and the subsequent risk of complications in patients with type 2 diabetes. Indeed, in an analysis from 2000 (and therefore not included in the current review) Muggeo et al. [28] reported that in type 2 diabetes insulin treatment was an independent risk factor for all cause mortality, although this may reflect patients with more advanced disease.

The studies identified here illustrate that a large number of different methods are currently used to assess glycemic variability and that the term may refer to either intra- or inter-day variability. Currently, there is no consensus on which, if any, method, represents the ''gold standard'' and most methods are associated with notable limitations. The majority of studies that have examined the degree of correlation between different assessment methods showed that most widely used methods are closely correlated with one another and with measures of overall glycemic control [6,22,23]. However, Cameron et al. [31] note that whilst different measures of glycemic variability are closely correlated in non-diabetes subjects correlation coefficients decreased significantly when the analysis was performed in patients with type 1 diabetes.

The most commonly used measures are the coefficient of variation of mean glucose or FPG levels or MAGE. Although SD is also widely used, it does carry a limitation, in that its use implies that glucose measures are normally distributed, which is typically not the case. The major limitation of the methods of measurement of glycemic variability associated with SMBG based measures is that they provide an unsophisticated measure of variability, with a significant dependence on patient cooperation that makes difficult the planning of long-term studies. For this reason, prospective studies with CGM use may be easily performed to provide valuable data with minimal inconvenience to the patient. Some investigators are strong proponents of the use of CGM for the assessment of glycemic variability and PPG excursions as well as selecting the most appropriate insulin regimen [32]. Additionally, long-term prospective studies using CGM would permit the investigation of the relative contribution of glycemic fluctuations in the development of long-term complications.

Overall, the low number of studies means that it is not possible to draw conclusions with any degree of certainty. Future large-scale studies are required, particularly in type 1 diabetes, as the majority of published studies to date have been performed using the same dataset, in order to fully elucidate the contribution of glycemic variability to the incidence and/or progression of long-term complications in patients with type 1 and type 2 diabetes. Additionally, a large proportion of studies, particularly in type 1 diabetes assessed glycemic variability using 7-point SMBG profiles, which offer a relatively crude measure of variability in comparison with CGM. As-mentioned earlier, prospective, long-term longitudinal studies using CGM would provide valuable information in relation to the role of glycemic variability in the development of diabetes complications and to establish whether patients with high levels of variability have increased risk for complications. Such studies would also help to further elucidate the nature of the complex relationship between post-prandial and fasting components of glycemia and glycemic variability, chronic sustained hyperglycemia and long-term complications.

The current review was not designed to investigate the association between glycemic variability and hypoglycemic events, although the use of CGM may provide valuable information in terms of the detection of hypoglycemic events. However, this relationship has been investigated in type 1 [29] and type 2 diabetes [33–35]. An analysis of DCCT data by Kilpatrick et al. [29] showed that in type 1 diabetes within day SD of mean blood glucose was an independent predictor of time to first severe hypoglycemic event. For type 2 diabetes, a French prospective observational study conducted using CGM, Monnier et al. [32] reported a significant association between higher SD of mean glucose and increased incidence of asymptomatic hypoglycemia. Similarly, two retrospective 24-week studies in type 2 diabetes showed that subjects with $\geq$1 hypoglycemic event had a significantly higher SD of blood glucose levels and MAGE versus those with no hypoglycemic events [35]. These findings in subjects with type 2 diabetes should be interpreted with caution as the risk for severe hypoglycemic events could have been influenced by treatment modality and duration of insulin therapy [36]. However, the association between glycemic variability and hypoglycemic events may have implications for the development of diabetes complications. The recent evidence from the large-scale ADVANCE and ACCORD studies suggests that hypoglycemia is associated with increased risk of vascular events and mortality [37–40].

Another issue that was not specifically addressed in the current review was that of variability in HbA1c as the present review focused on short-term measures of glucose variability and a full analysis of HbA1c variability is beyond the scope of the present review. However, several recent studies have investigated the association between variability in HbA1c and micro- and macrovascular complications. In type 2 diabetes, a number of studies have suggested that variability in HbA1c may be an important factor in the development of nephropathy [41–45]. Evidence on the role of HbA1c variability in the development of retinopathy and also macrovascular complications in type 2 diabetes is less consistent [41,42,46]. In type 1 diabetes, variability in HbA1c has been implicated in increasing the risk for microvascular complications [47–49] suggesting a role for long-term fluctuations in HbA1c and the development of nephropathy and retinopathy over and above that of mean HbA1c values alone.

In conclusion, 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 type 2 diabetes, but uncertainty remains as to whether it is a contributing factor in the development of macrovascular complications. In patients with type 1 diabetes, the role of increased short-term glucose variability in the development of both micro- and macrovascular complications is less evident. However, since the bulk of data in type 1 diabetes were derived from a single study (i.e. DCCT), further studies are required to establish if these findings are consistent across different type 1 diabetes populations.

Conflict of interest

This review was supported by funding from Medtronic International Trading Sàrl. Jayne Smith-Palmer and William Valentine are employees of Ossian Health Economics and Communications, which received funding from Medtronic International Trading Sàrl to carry out this review. Marco Orsini and Severine Liabat are employees of Medtronic. Michael Brändle and Roberto Trevisan have no conflict of interests to declare.

Appendix A. Literature search strategy

Search strategies used for the PubMed, Cochrane Library and EMBASE databases are presented in Tables A1–A3.

Table A1 – PubMed search strategy glycemic variability in patients with diabetes.

Line #	Search terms	Hits
#1	"*Diabetes Mellitus*" [MeSH] OR "*Diabetes Complications*" [MeSH]	279,843
#2	#1 AND "*Hypoglycemia*" [MeSH] OR "*Hyperglycemia*" [MeSH] OR "*Blood glucose*" [MeSH] OR "*Blood glucose*" [text] OR "*Glycemic control*" [text]	68,897
#3	#2 AND "*Glycemic variation*" [text] OR "*Glycemic variability*" [text] OR "*Glucose excursion*" [text] OR "*Glycemic excursion*" [text] OR "*Postprandial excursion*" [text] OR "*Glucose variability*" [text] OR "*Glucose variation*" [text] OR "*Continuous glucose monitoring*" [text]	1759
#4	#3 AND *English* [lang] and *Humans* [MeSH] and ("2002/06/25" [PDat]: "2012/06/21" [PDat]	1113

PubMed searches were conducted on June 21, 2012 and a total of 1113 records were identified.

Table A2 – Cochrane Library search strategy glycemic variability in patients with diabetes.

Line #	Search terms	Hits
#1	MeSH descriptor *Diabetes Mellitus* explode all trees	13,620
#2	#1 AND MeSH descriptor *Hypoglycemia* explode all trees OR MeSH descriptor *Hyperglycemia* explode all trees OR MeSH descriptor *Blood glucose* explode all trees OR *blood glucose*; ti,ab,kw OR *glycemic control*; ti,ab,kw	6532
#3	#2 AND ''*Glycemic variation*'' [text] OR ''*Glycemic variability*'' [text] OR ''*Glucose excursion*'' [text] OR ''*Glycemic excursion*'' [text] OR ''*Postprandial excursion*'' [text] OR ''*Glucose variability*'' [text] OR ''*Glucose variation*'' [text] OR ''*Continuous glucose monitoring*'' [text]	682
#4	#3 AND Published in the last 10 years	475

Cochrane Library searches were conducted on June 21, 2012 and a total of 475 records were identified.

Table A3 – EMBASE search strategy glycemic variability in patients with diabetes.

Line #	Search terms	Hits
#1	Exp *Diabetes Mellitus/*	505,975
#2	#1 AND Exp *hypoglycemia*/OR exp *hyperglycemia*/OR *exp glucose blood level*/OR *exp glycemic control*/	105,455
#3	#2 AND *Glycemic variation.tw.* OR *Glycemic variability.tw.* OR *Glucose excursion.tw.* OR *Glycemic excursion.tw.* OR *Post-prandial excursion.tw.* OR *Glucose variability.tw.* OR *Glucose variation.tw.* OR *Continuous glucose monitoring.tw.*	1764
#4	#3 AND Limit to (human and English language and published in the last 10 years)	1193

EMBASE searches were conducted on June 21, 2012 and a total of 1193 records were identified.

Appendix B. Inclusion and exclusion criteria

For inclusion studies were required to be published in English from 2002 to 2014. Additional exclusion criteria and definitions were as follows:

- Not presenting outcomes of interest – studies that either did not present short-term glycemic variability as an outcome, presented variability in HbA1c, or presented measures of variability but did not link these to the incidence or prevalence of long-term complications.
- Wrong publication type – articles that were classed as letters, commentaries, narrative reviews, or editorials.
- Pilot studies – studies with an enrollment of fewer than 50 patients.
- Wrong subject area – studies not in patients with type 1 or type 2 diabetes, includes general population studies and studies in gestational diabetes.
- Education/methods based study – studies describing education of health care professionals/patients in measurement of diabetes.
- Animal studies.
- Pharmacodynamic/pharmacokinetic or in vitro studies.

REFERENCES

[1] Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006;49:1711–21.

[2] Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. JAMA 2006;295:1707–8.

[3] Snell-Bergeon JK, Roman R, Rodbard D, Garg S, Maahs DM, Schauer IE, et al. Glycaemic variability is associated with coronary artery calcium in men with type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes Study. Diabet Med 2010;27:1436–42.

[4] Mi SH, Su G, Li Z, Yang HX, Zheng H, Tao H, et al. Comparison of glycemic variability and glycated hemoglobin as risk factors of coronary artery disease in patients with undiagnosed diabetes. Chin Med J (Engl) 2012;125:38–43.

[5] Service FJ. Glucose variability. Diabetes 2013;62:1398–404.

[6] Sartore G, Chilelli NC, Burlina S, Di Stefano P, Piarulli F, Fedele D, et al. The importance of HbA1c and glucose variability in patients with type 1 and type 2 diabetes: outcome of continuous glucose monitoring (CGM). Acta Diabetol 2012;49(Suppl. 1):S153–60.

[7] Dossett LA, Cao H, Mowery NT, Dortch MJ, Morris Jr JM, May AK. Blood glucose variability is associated with mortality in the surgical intensive care unit. Am Surg 2008;74:679–85.

[8] Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med 2008;36:3008–13.

[9] 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.

[10] The Diabetes Control and Complications Trial 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;44:968–83.

[11] Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial – revisited.DCCT/EDIC Research Group Diabetes 2008;57:995–1001.

[12] Pochinka I, Strongin L, Struchkova J. Glycaemic variability and ventricular cardiac arrhythmias in type 2 diabetic patients with chronic heart failure. In: 48th annual meeting of the European Association for the Study of Diabetes; 2012 [abstract].

[13] Mo Y, Zhou J, Li M, Wang Y, Bao Y, Ma X, et al. Glycemic variability is associated with subclinical atherosclerosis in Chinese type 2 diabetic patients. Cardiovasc Diabetol 2013;12(January (15)):15.

[14] Barbieri M, Rizzo MR, Marfella R, Boccardi V, Esposito A, Pansini A, et al. Decreased carotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. Atherosclerosis 2013;227(April (2)):349–54.
[15] Liu Y, He Y. Effect of blood glucose excursions on the risk of diabetic retinopathy in type 2 diabetes. In: 2011 Diabetes. Conference: 71st scientific sessions of the American Diabetes Association San Diego; 2011 [abstract].
[16] Liu Y, Li Y, Cai H, Zhang X. The relationship between glycemic variability and macrovascular and microvascular complications in type 2 diabetes. In: 2011 Diabetes. Conference: 71st scientific sessions of the American Diabetes Association San Diego; 2011 [abstract].
[17] Yang Y, Xu L, Feng X. A positive relationship of glycemic levels with the development of diabetic cardiomyopathy and serum CTGF level in patients with type 2 diabetes. In: 2011 Diabetes. Conference: 71st scientific sessions of the American Diabetes Association San Diego; 2011 [abstract].
[18] Mo Y, Zhou J, Li M, Wang Y, Bao Y, Ma X, et al. Glycemic variability is associated with subclinical atherosclerosis in type 2 diabetes. In: 12th Annual Diabetes Technology Meeting; 2012 [abstract].
[19] Zhong Y, Zhang XY, Miao Y, Zhu JH, Yan H, Wang BY, et al. The relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. Biomed Environ Sci 2012;25(February (1)):1–7.
[20] Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 2007;50:2239–44.
[21] 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 HbA(1c). Diabetes Care 2003;26:881–5.
[22] Kohnert KD, Augstein P, Heinke P, Zander E, Peterson K, Freyse EJ, et al. Chronic hyperglycemia but not glucose variability determines HbA1c levels in well-controlled patients with type 2 diabetes. Diabetes Res Clin Pract 2007;77:420–6.
[23] Kohnert KD, Augstein P, Zander E, Kohnert KD, Augstein P, Zander E, et al. Glycemic variability correlates strongly with postprandial beta-cell dysfunction in a segment of type 2 diabetic patients using oral hypoglycemic agents. Diabetes Care 2009;32:1058–62.
[24] Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens 2000;18: 655–73.
[25] 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;12:288–98.
[26] Siegelaar SE, Holleman F, Hoekstra JB, DeVries JH. Glucose variability; does it matter? Endocr Rev 2010;31:171–82.
[27] Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. 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;96:1750–4.
[28] Muggeo M, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, 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.
[29] Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007;50:2553–61.
[30] Lin CC, Li CI, Yang SY, Liu CS, Chen CC, Fuh MM, et al. Variation of fasting plasma glucose: a predictor of mortality in patients with type 2 diabetes. Am J Med 2012;125:416.e9–416.e18.
[31] Cameron FJ, Donath SM, Baghurst PA. Measuring glycaemic variation. Curr Diabetes Rev 2010;6:17–26.
[32] Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? J Diabetes Sci Technol 2008;2:1094–100.
[33] Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. Diabetes Technol Ther 2011;13:813–8.
[34] Niskanen L, Virkamäki A, Hansen JB, Saukkonen T. Fasting plasma glucose variability as a marker of nocturnal hypoglycemia in diabetes: evidence from the PREDICTIVE study. Diabetes Res Clin Pract 2009;86:e15–8.
[35] Inzucchi SE, DiGenio A, Zhou R, Umpierrez G. The impact of glucose variability on achievement of glycaemic control and risk of hypoglycaemia in patients with type 2 diabetes. In: Diabetologia. Conference: 47th annual meeting of the European Association for the Study of Diabetes, EASD; 2011 [abstract].
[36] Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34:S132–7.
[37] Lipska KJ, Kosiborod M. Hypoglycemia and adverse outcomes: marker or mediator? Rev Cardiovasc Med 2011;12:132–5.
[38] Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–8.
[39] Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff Jr DC, Peterson K, et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care 2012;35:409–14.
[40] Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909.
[41] Luk AO, Ma RC, Lau ES, Yang X, Lau WW, Yu LW, et al. Risk association of HbA1c variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2013;29(July (5)):384–90.
[42] Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care 2013;36(August (8)):2301–10.
[43] Hsu CC, Chang HY, Huang MC, Hwang SJ, Yang YC, Lee YS, et al. HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study. Diabetologia 2012;55(December (12)):3163–72.
[44] Rodríguez-Segade S, Rodríguez J, García López JM, Casanueva FF, Camiña F. Intrapersonal HbA(1c) variability and the risk of progression of nephropathy in patients with type 2 diabetes. Diabet Med 2012;29(December (12)):1562–6.
[45] Sugawara A, Kawai K, Motohashi S, Saito K, Kodama S, Yachi Y, et al. HbA(1c) variability and the development of microalbuminuria in type 2 diabetes: Tsukuba Kawai Diabetes Registry 2. Diabetologia 2012;55(August (8)): 2128–31.
[46] Penno G, Solini A, Zoppini G, Orsi E, Fondelli C, Zerbini G, et al. Hemoglobin A1c variability as an independent correlate of cardiovascular disease in patients with type 2 diabetes: a cross-sectional analysis of the renal

insufficiency and cardiovascular events (RIACE) Italian multicenter study. Cardiovasc Diabetol 2013;12(July (5)):98.
[47] Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care 2008;31:2198–202.
[48] Hietala K, Wadén J, Forsblom C, Harjutsalo V, Kytö J, Summanen P, et al. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia 2013;56(April (4)):737–45.
[49] Hermann JM, Hammes HP, Rami-Merhar B, Rosenbauer J, Schütt M, Siegel E, et al. HbA1c variability as an independent risk factor for diabetic retinopathy in type 1 diabetes: a German/Austrian multicenter analysis on 35,891 patients. PLoS ONE 2014;9(March (3)):e91137.
[50] Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care 2006;29:1486–90.
[51] Kilpatrick ES, Rigby AS, Atkin SL. Effect of glucose variability on the long-term risk of microvascular complications in type 1 diabetes. Diabetes Care 2009;32:1901–3.
[52] Siegelaar SE, Kilpatrick ES, Rigby AS, Atkin SL, Hoekstra JB, Devries JH. Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT. Diabetologia 2009;52:2229–32.
[53] Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia 2008;51:365–71.
[54] Houssay S, Alvarinas JH, Burlando G, Gonzalez C, Garcia A, Vasta S. The relation of heart rate variability with glycemic variability in type 1 diabetic patients. In: 2011 Diabetes. Conference: 71st scientific sessions of the American Diabetes Association San Diego; 2011 [abstract].
[55] Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. Acta Diabetol 2013;50(June (3)): 437–42.
[56] Siegelaar SE, Kerr L, Jacober SJ, Devries JH. A decrease in glucose variability does not reduce cardiovascular event rates in type 2 diabetic patients after acute myocardial infarction: a reanalysis of the HEART2D study. Diabetes Care 2011;34:855–7.
[57] Su G, Mi S, Tao H, Li Z, Yang H, Zheng H, et al. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovasc Diabetol 2011;10:19.
[58] Takao T, Ide T, Yanagisawa H, Kikuchi M, Kawazu S, Matsuyama Y. The effect of fasting plasma glucose variability on the risk of retinopathy in type 2 diabetic patients: retrospective long-term follow-up. Diabetes Res Clin Pract 2010;89:296–302.
[59] Abbatecola AM, Rizzo MR, Barbieri M, Grella R, Arciello A, Laieta MT, et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology 2006;67:235–40.
[60] Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. J Diabetes Sci Technol 2009;3:1292–301.
[61] Gimeno-Orna JA, Castro-Alonso FJ, Boned-Juliani B, Lou-Arnal LM. Fasting plasma glucose variability as a risk factor of retinopathy in type 2 diabetic patients. J Diabetes Complications 2003;17:78–81.
[62] Klindukhova O, Chandra P, Ping L. Glycemic variability and clinical outcomes in general surgery patients. In: 2011 Diabetes. Conference: 71st scientific sessions of the American Diabetes Association San Diego; 2011 [abstract].
[63] Takao T, Ide T, Yanagisawa H, Kikuchi M, Kawazu S, Matsuyama Y. The effects of fasting plasma glucose variability and time-dependent glycemic control on the long-term risk of retinopathy in type 2 diabetic patients. Diabetes Res Clin Pract 2011;91:e40–2.
[64] Zoppini G, Verlato G, Targher G, Casati S, Gusson E, Biasi V, et al. Is fasting glucose variability a risk factor for retinopathy in people with type 2 diabetes? Nutr Metab Cardiovasc Dis 2009;19:334–9.