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GLYCEMIC KEY METRICS AND THE RISK OF DIABETES-ASSOCIATED COMPLICATIONS

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Abstract

Prevention of diabetes-associated complications is closely linked to preventing and controlling hyperglycemia. Glycated hemoglobin (HbA1c), a glucose metric and a risk factor for chronic complications, is not reliable under certain clinical conditions, does not capture glyemic variability and glucose dynamics. There is evidence that glycemic variability is an independent predictor variable of hypoglycemia and a potential risk marker for vascular diabetes complications. Despite advanced glucose monitoring methods, monitoring of glucose with blood glucose meters remains indispensible as an adjunct to HbA1c measurements, because it gives direct feedback on short-term changes in glucose levels. Optimized diabetes treatment and prevention or delay of diabetes complications needs both key glucose control metrics on a daily basis, involving fasting, preprandial, and postprandial glucose levels as well as advanced, user-friendly monitoring methods. The broad application of systems for continuous glucose monitoring in clinical settings is partly hampered by lacking measures generally accepted for analysis of glucose profiles and as standards for reporting of glucose data. We performed a literature search, using PubMed and Scopus and included relevant literature published online up to March 1, 2016. In this review, we discuss the importance of several glucose measures for primary and secondary prevention of diabetes complications and possibilities for evaluation of monitored glucose data with special consideration of glycemic variability, glucose dynamics, and the utility of continuous glucose monitoring.

key words: *diabetes complications, glycemic control markers, hemoglobin A1c, glycemic variability, dynamical glucose complexity*

Introduction

High levels of glucose can damage a variety of cells—an effect known as glucotoxicity. Thus, diminishing glucotoxicity by tight glycemic control is crucial for optimizing treatment of diabetes. Evidence has been provided by landmark trials that chronic sustained hyperglycemia is related to vascular diabetes complications. But the mechanisms how hyperglycemia gives rise to the development of disease complications is different for type 1 (T1D) and type 2 diabetes (T2D). Intensive control of glycemia, if started in T1D patients with short disease duration, resulted in recovery of pancreatic ß-cells and reduced micro- and

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macrovascular morbidity [1]. And in T2D, lowering of glucose protects against microvascular complications, cataracts, and neuropathy but has shown only modest effects on reduction of cardiovascular diabetes complications [2]. There is no doubt however, that tight control of glycemia early after the disease onset has a durable effect (legacy effect) on complications. Thus, standardized glycemic biomarkers are required, which should also be useful as surrogate measures to assess the risk of late complications of diabetes.

The results of The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Pereterax[g] + Diamicron Modified Release Controlled Evaluation (ADVANCE) trials suggested that levels of hemoglobin A1c (HbA1c) should be individualized according to the patients´ health status to prevent hypoglycemia; patients with older age and extensive comorbidities require less rigorous target levels [3]. In a post-trial evaluation (ADVANCE-ON), strict glucose control was also associated with long-term reduced end-stage kidney disease [4]. Although HbA1c levels predict long-term outcomes and correlate with morbidity and mortality in people with T1D and T2D, associations with macrovascular end points were weaker than with microvascular end points. And we have shown in previous studies that the risk of peripheral vascular disease increases significantly when HbA1c values were >8.0% (63.9 mmol/mol) [5]. But, how measures of glycemia can reliably predict late diabetes complications, or whether several markers used in combination, might be more effective to indicate adverse outcomes than a single biomarker, remains still unclear. Data provided by the Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complication (DCCT/EDIC) Study support recent suggestions of using two markers to strengthen risk prediction [6]. A combination of short- and long-term markers of glycemia, including glucose variability (GV) and glucose dynamics, might be more powerful to predict cardiovascular outcomes. Moreover, HbA1c measurement supplemented with new markers should allow both better assessment of glycemia and prediction of diabetic complications.

The present review focuses on the importance of choosing those markers most relevant to optimize management of diabetes and to prevent late diabetes complications.

By using PubMed and Scopus, this literature search comprises the pertinent literature published online up to March 1, 2016, and considered guidelines of the international Diabetes Associations.

Key markers of glycemic control and potential risk predictors

Glycemic biomarkers are a prerequisite for guiding diabetes therapy in clinical practice and serve as surrogate measures for diabetes complications (Table 1). In addition to HbA1c, fructosamine and glycated albumin may provide advantages under specific clinical situations. These markers, will not be dealt with in the present review; they reflect shorter-term glycemic control than HbA1c.

Table 1. Glucose metrics as potential risk predictors of diabetes complications.

Marker	Complication	Reference
Hemoglobin A1c	Cardiovascular disease Cardiovascular disease Nephropathy Retinopathy	Khaw and Wareham 2006 [7] Nathan et al. 2014 [6]

Table 1. *Continued*

Marker	Complication	Reference
Hemoglobin A1c	Dementia	Rawshani et al. 2015 [8]
	End-stage kidney disease	Wong et al. 2016 [4]
Mean glucose	Cardiovascular disease	Borg et al. 2011 [9]
Fasting glucose	Cardiovascular disease	Barr et al. 2007 [10]
		Monami et al. 2013 [11]
Postprandial glucose	Cardiovascular disease	Esposito et al. 2008 [12]
		Raz et al. 2009 [13]
		Cavelot et al. 2011 [14]
Glycemic variability	Microvascular disease Diabetic kidney disease	Kilpatrick et al. 2008 [15] Vaduva et al. 2013 [16]
	Cardiovascular disease	Su et al. 2011 [17]
	Any microvascular disease	Soupal et al. 2014 [18]
	Major micro- and macrovascular events	Hirakawa et al. 2014 [19]
	Peripheral neuropathy	Bragd et al. 2008 [20]
		Xu et al. 2014 [21]

HbA1c

Hemoglobin is a protein molecule; and its nonenzymatic glycation can occur at several amino acid residues. The glycation process is slow, depends on the ambient glucose concentration, and results in several adducts of hemoglobin A. HbA1c, being the most important component among the hemoglobin adducts, is considered the gold standard for long-term glycemic control and guiding diabetes therapy in conjunction with self-monitored blood glucose (SMBG). The HbA1c analysis from dried blood samples has increased the availability of testing [22]. Moreover, the International Expert Committee (IEC) report 2009 confirmed use of HbA1c for the diagnosis of diabetes. The utility of HbA1c for long-term control of glycemia and as surrogate measure for the development of diabetes complications has been well documented (Table 1). However, HbA1c is a measure of long-term glucose exposure; it integrates fasting, pre-prandial as well as postprandial hyperglycemic excursions. The proportional contribution of these domains of dysglycemia to HbA1c levels is dependent on the quality of glycemic control [23].

The close relationship between HbA1c and sustained chronic hyperglycemia convinced the International Federation of Clinical Chemistry and the International Diabetes Federation to endorse reporting of HbA1c as estimated average glucose (eAG), which helps management of diabetic patients [24]. Furthermore, HbA1c is the most often used surrogate endpoint in clinical studies, because it evidently predicts the appearance of diabetes complications in the course of the disease. Khaw and Wareham reported that a 1% incremental increase in HbA1c is equivalent to about 10-20% enhanced cardiovascular risk [7]. Prospective cohort studies confirmed these outcomes in 48,444 people with T2D [25] and in older diabetes patients [26]. More recently, a large observational study in 363,573 patients with T2D found that HbA1c was positively associated with dementia [8]. But further insight into the diabetes pathogenesis, has revealed significant limitations of using HbA1c measurements, such that identical HbA1c values can reflect different concentrations of mean glucose [27,28]. Thus, wide variations in mean glucose can occur between and within patients such that HbA1c levels do not always match the clinical situation.

The mismatches might chiefly be explained by differences in intracellular glycation rates (glycation gap) [29]. In about 15-25% of patients, overall glycemia is not adequately reflected by HbA1c levels. Among the various clinical conditions that could interfere with HbA1c measurements are, for example, high red cell turnover, hemolytic disorders, blood transfusion, chronic diseases of kidneys or liver [28], and drug treatment. These circumstances require glycated albumin or fructosamine to be considered as alternative control metrics. Another limitation of HbA1c is certainly the lacking, respectively, weak correlation with hypoglycemia and glycemic variability (GV). HbA1c is strongly correlated with chronic sustained hyperglycemia [30], whereas glycemic excursions largely escape detection, as indicated by the small correlation coefficients with commonly used GV metrics. This seems to be critical for clinical decisions and especially for adjustment of insulin therapy in some diabetic patients.

The use of fasting, postprandial, and mean glucose

Besides HbA1c measurement, estimation of glucose exposure may be useful for monitoring the effects of exercise, food intake, and efficacy of antidiabetic medications. Both fasting (FBG) and postprandial blood glucose (PPG) are measures for individual assessment of glycemic control and allow lifestyle modification, even though the relative contributions of the two measures change with increasing HbA1c values [31]. Figure 1 shows that, as patients approach their glycemic target (HbA1c < 7.0%), PPG plays a greater part than FPG in the overall glycemia.

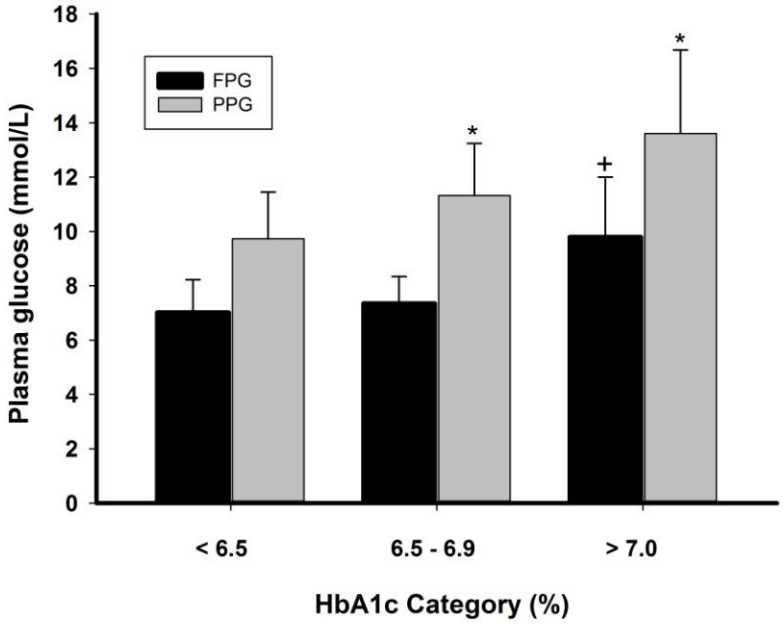

Figure 1. *Relative contribution of fasting (FPG) and postprandial plasma glucose (PPG) to the overall diurnal glycemia over HbA1c categories in a cohort of non-insulin treated patients with T2D (n = 114, mean age 63.5 years, mean diabetes duration 6.9 years). Statistically significant differences observed between <6.5% and the two higher HbA1c categories in PPG levels (*p < 0.01) and in FPG ($^{+}p < 0.001$, two-tailed t-test). Data source: Kohnert et al. unpublished data.*

About the relationship of FPG or 2h plasma glucose (PG) with regard to diabetes mortality, the data from the Baltimore Longitudinal Study on Aging indicated that levels of FPG, exceeding 7.0 mmol/l, increased the mortality risk; and the 2hPG, if added, augments the predictive power

to that of FPG alone [32]. Also in the Australian Diabetes, Obesity, and Life Style Study [10], impaired fasting glucose emerged as an independent predictor for cardiovascular mortality. A recent meta-analysis showed that lowering of FPG levels was related with decreased cardiovascular mortality, and PPG data pointed in the same direction [11]. Furthermore, observational studies showed that high PPG concentrations increased the risk of cardiovascular events approximately threefold [33]. The Diabetes Intervention study [34] in T2D disclosed the deleterious relationship between increased PPG levels (>10 mmol/l) and higher risk of cardiovascular events; while reduction below this level was shown to decrease rates of myocardial infarction and death. That PPG was a stronger predictor of cardiovascular events than FPG was confirmed in an excellent follow-up study [14], where postmeal incremental glucose values >2.78 mmol/l significantly correlated with increased carotid intima-media thickness [12]. The concept of treating pathologically elevated PPG to prevent cardiovascular complications was supported by a post-hoc analysis of the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study [13]. However, it is not yet clarified whether PPG represents a real marker for cardiovascular diabetes complications or merely a surrogate of metabolic processes, occurring in the postprandial phase. Nevertheless, this measure is helpful to appraise the magnitude of meal-induced glucose excursions and the efficacy of diabetes treatment. Note that pre-meal hyperglycemia contributes to PPG, and considering both will help patients to reach their glycemic targets [35]. The American Diabetes Association and International Diabetes Federation emphasize PPG and recommend PPG values ≤10.0 and respectively ≤9.0 mmol/l [36,37].

When it comes to assessment of actual glucose exposure, mean glucose (average glucose) is a suitable metric that allows easy evaluating the quality of diabetes control by both clinicians and patients over shorter time intervals than with HbA1c. And it is closely correlated with the risk of cardiovascular diabetes complications [9].

Measures of glucose variability

Clinical observations in continuously-monitored subjects with TD1 and TD2, even if they present with good glycemic control, disclosed that glucose profile dynamics can greatly differ. The ups and downs in glucose levels can be classified as within-day and between-day glycemic variability (GV). Several indices that are currently available characterize various aspects of glucose fluctuations [38]. Although they can principally be calculated from seven- or eight-point SMBG profiles, it is advisable to use continuous glucose monitoring (CGM) data to capture all relevant peaks and nadirs in the CGM profiles. Not unexpectedly, the magnitude of GV depends on the sampling frequency [39]; and low frequencies cause erroneous results. The mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), and continuous overall net glycemic action (CONGA) are the GV metrics, which should preferably be used for clinical research. Several computer programs have been developed to ease calculation of GV indices. For practical reasons, an expert panel of diabetes specialists [40] recommended two of the known metrics: SD (standard deviation) around the mean glucose (SD) and interquartile range (IQR). IQR is the most reliable aggregate measure of GV, as announced by the panel of experts. Nevertheless, these metrics are

dependent on mean glucose and HbA1c level. The percentage coefficient of variation (%CV) does not have these drawbacks and correlates equally well with time in hyper- and hypoglycemia; it was recommended rather for clinical research than for routine practice. Furthermore, it must clearly be distinguished between measures of GV and those measures, characterizing the quality of glucose control.

Concerning the clinical importance of GV, it remains yet controversial whether this factor is causative or contributing to diabetes complications [41]. There are only a few studies that suggest GV to affect microvascular complications in patients with T1D [42]. GV measured by SD was predictive of peripheral neuropathy [20,21], and subclinical atherosclerosis was reported to be correlated with glucose levels and glucose SD [43]. The potential importance of GV indices such as SD, CV, and MAGE for microvascular complications in T1D has recently been suggested by Šoupal et al. [18]. Note that the Diabetes Control and Complications Trial results revealed that fluctuations in glucose levels measured as SDs of HbA1c are independently related to retinopathy and nephropathy [15]. A more recent study in patients with T2D has identified HbA1c variability as predictive of all-cause mortality [44]. There are more study data available for T2D than for T1D that demonstrate significant associations between GV and vascular complications [45]. Among the well-established indices, increased MAGE has been reported as possible risk factor for microalbuminuria in well-controlled patients [46]. Văduva et al. [16] observed higher GV in T2D patients suffering from chronic kidney disease than in those having no detectable kidney damage. In insulin-treated diabetes patients, GV was higher during hemodialysis compared with the hemodialysis-free intervals [47]. Regarding macrovascular complications of diabetes, significant associations were found between MAGE and progression of atherosclerosis [48]. These latter results support the value of GV metrics in predicting major adverse cardiac events and their severity in established T2D [17]. The role of GV was strengthened by the analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial (ADVANCE). This study provided data for a clear association that existed between SD of glucose and all-cause mortality [19]. GV indices, with the exception of the coefficient of variation (%CV), do correlate with mean glucose; thus, it remains uncertain whether GV plays an independent role in the development of diabetes complications. Ratios such as SD/mean glucose x 100 (%CV) or MAGE/mean glucose x 100 might help to circumvent dependence on glucose levels. In clinical practice, SD and IQR can safely be used to sufficiently adjust glycemic stability without enhancing the time in hypoglycemia.

Indices of glucose dynamics

The preceding glucose metrics, including GV, are derived from linear analysis of glucose data; thus, contributing insufficient information to glucose dynamics. A reduced glucose complexity was reported in the transition from normoglycemia to overt diabetes, using detrended fluctuation analysis (DFA) [49]. Likewise, the Poincaré plot analysis of glucose time series is a useful tool to measure temporal glycemic variability, in which the length of the minor SD1 and major SD2 axes of the plot correspond to short-term and long-term variability, respectively. Crenier [50] extended the application of Poincaré plots by validating new metrics, e.g. area and shape of the fitting ellipse. One may speculate whether glucose dynamics, that is glucose complexity,

contributes independently to the progress of diabetes complications; however, analyzing glucose time series at multiple time scales would provide a closer approach than using traditional GV indices. Beyond traditional estimates, glucose complexity measures have the potential to assess treatment modalities toward improving the dynamics of the glucoregulatory system. The multiscale entropy (MSE) approach represents a predominating method to characterize the complexity of physiological signals and has recently been introduced for assessment of glucose dynamics (dynamical glucometry) in diabetes [51].

Glucose monitoring

Although the glucose monitoring techniques have rapidly advanced, self-monitoring of blood glucose (SMBG) with hand-held glucose meters and maintaining tight standards is still the primary technique to assess glycemic control in routine diabetes management [52]. However, SMBG measures single glucose values and provides only snapshots – rapid changes almost escape detection. CGM systems have expanded during recent years, but standardized metrics are still lacking. An expert panel proposed the Ambulatory Glucose Profile (AGP) "Dashbord" and glucose profile summary metrics for better utilization of glucose data in clinical practice [40]. Time in range (TIR), either expressed as "% of glucose readings" or "hours per day", was identified as a key metric for guiding diabetes treatment. The blood glucose range 3.9-10.0 mmol/l was selected for clinical practice as the default target range. If required, individualized targets should be envisaged according to patient age, comorbidities, and compliance. The key metrics agreed upon, are summarized in Table 2. Although primarily intended for CGM, they can also be used with advanced blood glucose meters.

Table 2. Key glucose metrics for guiding treatment of diabetes.

Glycemic domains	Metrics/Defaults	Clinical information
Glycemic exposure	HbA1c	Long-term glycemic control
	Mean/median glucose	Exercise, food, insulin dosage effects
Glycemic ranges	Time in range 3.9-10.0 mmol/l	Actual glucose status
	Time above 10.0 mmol/l	Risk of diabetic ketoacidosis
	Time below 3.9 mmol/l	Risk of severe hypoglycemia
Glycemic variability	Interquartile range	Risk of hyper-hypoglycemia
	SD of mean glucose	

Based on the recommendations presented by an Expert Panel of Diabetes Specialists, Tampa (FL) USA, March 28-29, 2012. [40]

The technology of CGM has become indispensible in the modern management of diabetes by producing glycemic profiles over several days or weeks, real-time glucose values, glucose trends and warnings when glucose values tend to increase to dangerously low or high levels [53]. In principle, the following system variants are available: retrospective (blinded glucose data) and real-time glucose monitoring. Flash glucose monitoring (FGM), a more recent technological development, offers advantages over traditional CGM systems. Regardless which systems is applied, they all require counseling and experience for both health care professionals and patients. Because CGM and FGM systems are based on subcutaneous measurements, the kinetics of the glucose sensing is mainly defined by physiological processes in the subcutaneous space. If glucose sensing is done in the peritoneal space, as recently reported, glucose monitoring can be optimized, because of faster

intra-peritoneal kinetics [54]. Preferably, pump-treated patients inclined to hypoglycemia and/or hypoglycemia unawareness will benefit from CGM. FGM circumvents frequent finger-stick glucose measurements by scanning the sensor and is useful for T1D and T2D patients on intensified conventional insulin therapy.

Conclusions

Although glucose monitoring technologies are advancing, HbA1c will continue to be the metric of choice for long-term glycemic control and as a surrogate measure for diabetes complications. But if clinical practice necessitates, it may be supplanted by other parameters. To obviate misinterpretation, HbA1c values should be given both in % and mmol/mol. It is important to take into consideration that glycated serum proteins can be alternative markers under clinical situations, which interfere with HbA1c measurements. In a number of diabetes patients with HbA1c <7% (<53 mmol/mol), indicating apparently good glycemic control, high postmeal incremental glucose values are not unexpected; thus, it is warranted to integrate measurements of pre-meal and PPG into routine diabetes control. Notably GV needs to be integrated into diabetes management. Since the GV metrics are known to be highly interrelated, any currently validated index can be applied for quantification of glucose fluctuations. Commonly used indices are MAGE and SD of glucose; however, %CV is independent of mean glucose and correlates with hypoglycemia. Based on our experience, we recommend mean glucose, TIR and PPG as short-term indicators, for management of glycemic control. In addition to these metrics, we recommend SD of the mean glucose, IQR, and %CV as indices of GV. Nevertheless, a combination of shorter- and longer-term glycemic markers might be preferable for assessment of metabolic control and prediction of vascular outcomes. Finally, glycemic control appears insufficient without integration of dynamic measures. Although current metrics of glucose dynamics cannot be judged at this stage, they have promising potential to obtain more insight into the glucoregulatory mechanisms, hitherto not gained with metrics commonly used.

The importance of GV and/or changes in glucose dynamics remains as yet unclear. However, one should be aware that other factors than simply high blood glucose levels are likely involved in glycemic control and complications of diabetes.

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