TOPIC HIGHLIGHT

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Utility of different glycemic control metrics for optimizing management of diabetes

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Abstract

The benchmark for assessing quality of long-term glycemic control and adjustment of therapy is currently glycated hemoglobin (HbA1c). Despite its importance as an indicator for the development of diabetic complications, recent studies have revealed that this metric has some limitations; it conveys a rather complex message, which has to be taken into consideration for diabetes screening and treatment. On the basis of recent clinical trials, the relationship between HbA1c and cardiovascular outcomes in long-standing diabetes has been called into question. It becomes obvious that other surrogate and biomarkers are needed to better predict cardiovascular diabetes complications and assess efficiency of therapy. Glycated albumin, fructosamin, and 1,5-anhydroglucitol have received growing interest as alternative markers of glycemic control. In addition to measures of hyperglycemia, advanced glucose monitoring methods became available. An indispensible adjunct to HbA1c in routine diabetes care is self-monitoring of blood glucose. This monitoring method is now widely used, as it provides immediate feedback to patients on short-term changes, involving fasting, preprandial, and postprandial glucose levels. Beyond the traditional metrics, glycemic variability has been identified as a predictor of hypoglycemia, and it might also be implicated in the pathogenesis of vascular diabetes complications. Assessment of glycemic variability is thus important, but exact quantification requires frequently sampled glucose measurements. In order to optimize diabetes treatment, there is a need for both key metrics of glycemic control on a day-to-day basis and for more advanced, user-friendly monitoring methods. In addition to traditional discontinuous glucose testing, continuous glucose sensing has become a useful tool to reveal insufficient glycemic management. This new technology is particularly effective in patients with complicated diabetes and provides the opportunity to characterize glucose dynamics. Several continuous glucose monitoring (CGM) systems, which have shown usefulness in clinical practice, are presently on the market. They can broadly be divided into systems providing retrospective or real-time information on glucose patterns. The widespread clinical application of CGM is still hampered by the lack of generally

accepted measures for assessment of glucose profiles and standardized reporting of glucose data. In this article, we will discuss advantages and limitations of various metrics for glycemic control as well as possibilities for evaluation of glucose data with the special focus on glycemic variability and application of CGM to improve individual diabetes management.

Core tip: Hemoglobin A1c is the gold standard to assess glycemic control and a surrogate for diabetes-associated complications. Self-monitoring of blood glucose complements daily diabetes management but is insufficient in providing complete information on short-term changes in glucose levels induced by effects of food or antidiabetic medication. Key metrics beyond HbA1c are needed for glycemic control on a day-to-day basis as well as more advanced monitoring methods. Herein, we will review advantages and limitations of different metrics for glycemic control as well as possibilities for characterization of glucose dynamics with the special focus on glycemic variability and continuous glucose monitoring.

INTRODUCTION

Since landmark studies have provided evidence that glycated hemoglobin (HbA1c) is linked to vascular complications of diabetes[1,2], this biomarker of glycemia emerged as the benchmark for current diabetes management. Thus, optimal diabetes control aims to restore levels of HbA1c to as normal as possible to reduce or prevent diabetic complications. However, HbA1c has some important limitations and is a rather complex measure of hyperglycemia. It represents an indicator for overall glucose exposure, integrating fasting, preprandial as well as postprandial hyperglycemia, but their relative contribution varies with the quality of glycemic control[3]. Apart from several medical conditions that can cause inaccurate test results, HbA1c neither captures glucose fluctuations nor does it provide any information on glucose dynamics.

Chronic sustained hyperglycemia is well known to increase the risk for micro- and macrovascular compli-

cations in type 1 as well as in type 2 diabetes. Especially postprandial/postchallenge hyperglycemia, independent of HbA1c or fasting glucose, has been associated with cardiovascular disease[4], and this could be confirmed very recently in a post-hoc analysis of the "Effects of prandial *vs* fasting glycemia on cardiovascular outcomes in type 2 diabetes (HEART2D)" study[5].

As generally accepted and laid down in the American Diabetes Association (ADA) and International Diabetes Federation (IDF) guidelines, strict glycemic control, implicating comprehensive diabetes evaluation, is needed to prevent or delay diabetes complications. Nevertheless, the outcomes of the ACCORD[6] and ADVANCE[7] trials have taught us that HbA1c levels should be tailored to the patients' health status-older age and extensive comorbid conditions require less stringent targets. In the overwhelming majority of large clinical trials, HbA1c has been used to predict long-term outcomes related to morbidity and mortality in people with type 1 and type 2 diabetes, but the strength of association with macrovascular end points was weaker than with microvascular end points. Furthermore, it remains still unclear how various measures of glycemia predict diabetes complications and whether a combination of several markers might even be more strongly related to adverse outcomes than a single biomarker. A recent analysis of data from the Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complication Study by Nathan *et al*[8] supports the suggestion of using two glycemic markers to strengthen risk prediction. Thus, it would not be surprising if in the near future a combination of shorter and longer term glycemic markers could be used to predict cardiovascular outcomes more precisely. Now, we believe that time has come to move from measurement of HbA1c to other markers, allowing for assessment of short-time and intermediate-time changes in glycemia.

Although self-monitoring of blood glucose (SMBG) is still the predominant mode of glucose monitoring, the use of advanced technology, such as continuous glucose monitoring (CGM) has shown remarkable benefits and expanded significantly during recent years. One of the major problems in utilization such systems are appropriate evaluation of the great amount of data provided by CGM and the lack of standardization.

The purpose of the present review is to give an insight into the problems of choosing the most relevant markers of glycemic control and how to evaluate CGM data properly to optimize management of diabetes in order to avoid long-term complications.

MARKERS OF GLYCEMIC CONTROL

Glycemic markers are indispensable in routine practice as well as in clinical trials to guide therapy and to investigate the efficacy of medications on patients' glycemic control. A summary of useful glucose measures is shown in Table 1. As discussed in the following, not only do these markers cover different timeframes of glycemic control,

Table 1 Traditional and alternative markers of glycemic control

Marker	Time span of glycemic control	Ref.
Hemoglobin A1c	1-3 mo	Cohen[15], 2007
Glycated serum proteins	2-3 wk	Takahashi *et al*[33], 2007
1,5-Anhydroglucitol	1-2 wk	Dungan *et al*[43], 2008
Glycemic variability indices	24-72 h	Rodbard[54], 2009
Mean plasma glucose	24-72 h	Bergenstal *et al*[30], 2013
Fasting plasma glucose	8-10 h	Monami *et al*[22], 2013
Postprandial plasma glucose	2-4 h	Standl *et al*[23], 2011

they also provide different information on glucose metabolism and may reflect different pathways.

HbA1c

HbA1c is formed by nonenzymatic glycation as adduct of glucose and the hemoglobin molecule. The HbA1c value reflects average glucose over 1-3 mo. The National Glycohemoglobin Standardization Program is the organization that evaluates, sets standards for accuracy, and certifies methods for measurement of HbA1c. Besides laboratory tests, even home monitors for patients have been approved, *e.g.*, Bayer A1cNow Selfcheck At-HomeA1c System or BioRad's Micromat™ Ⅱ Hemoglobin Instrument.

HbA1c has been used as a biomarker for more than three decades as universally accepted means for monitoring glycemic control and as clinical surrogate endpoint in diabetes. In both patients with type 1 and type 2 diabetes, it is well documented that HbA1c predicts the occurrence of diabetes complications. A review by Khaw *et al*[9] examined HbA1c as a risk predictor for cardiovascular disease and found that a 1% increment in absolute concentration of HbA1c was associated with about 10%-20% increase in cardiovascular risk[9]. Elley *et al*[10] confirmed in a large prospective cohort study of 48444 people with type 2 diabetes that increased HbA1c is an independent risk factor for cardiovascular disease, after adjusting for traditional risk factors. This is consistent with work by Ma *et al*[11] who suggested from data of a retrospective study in older patients with diabetes that elevated HbA1c values are an independent predictor of complex coronary lesions. However, a very recent analysis in subjects without diabetes and cardiovascular disease obtained little additional benefit for prediction of first-onset cardiovascular disease[12]. Prior to the Emerging Risk Factors Collaboration study[12] large trials, such as ACCORD[6] and ADVANCE[7], also failed to demonstrate the ability to alter cardiovascular outcomes upon lowering HbA1c values in patients with long-standing diabetes. This is in contrast to the effects of tight glycemic control in reducing microvascular complications. As a corollary, the uncertainty around HbA1c results in relation to clinical outcomes was augmented. Moreover, deeper
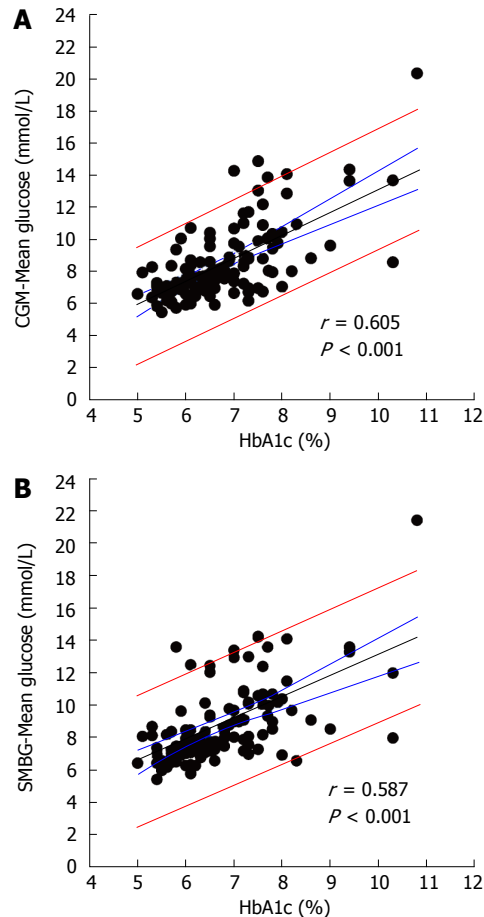

Figure 1 Relationship between hemoglobin A1c and mean glucose obtained from (A) continuous glucose monitoring and (B) self-monitoring of blood glucose in a cohort of 114 non-insulin treated type 2 diabetic patients. Medians (25th-75th percentile) for age, diabetes duration, and HbA1c were 59.0-68.0 yr, 2.0-10.0 yr, and 6.0%-7.3% (42-56 mmol/mol), respectively. The lines denote the regression lines (black), 95%CI (blue), and prediction intervals (red) (Kohnert *et al*, Unpublished data). CGM: Continuous glucose monitoring; HbA1c: Hemoglobin A1c.

insight into the pathogenesis of diabetes has disclosed important limitations of HbA1c measurement. For example, early analyses recognized that diabetic patients with identical HbA1c values can have different mean glucose concentrations[13,14]. The regression analysis shown in Figure 1 for a cohort of our type 2 diabetic patients demonstrates that although the regression coefficients between HbA1c and mean glucose obtained either from CGM or concurrent SMBG measurements are similar (Kohnert *et al,* Unpublished); wide variations in the relationship among and within the patients can be seen. In a minority of patients such mismatch might partly be explained by unequal temporal distribution of glucose sampling, but more importantly, there are studies to provide evidence that this observation is due to differences in intracellular glycation rates[15]. It appears that glycation of hemoglobin is not simply a concentration-dependent process, and factors other than glucose are likely to be involved. Moreover, conditions that could interfere with HbA1c measurement, causing erroneous values, are high red cell turnover, hemolytic anemia, blood

transfusion, chronic renal or liver disease[16], and drug treatment. Under these circumstances, HbA1c cannot be used as a glucose control measure; and alternative markers should be considered. The most important limitation of HbA1c is its inability to predict hypoglycemia and to capture short-term changes of glycemia. Furthermore, we have previously shown that in well-controlled patients with type 2 diabetes, HbA1c is mainly determined by chronic sustained hyperglycemia; glycemic fluctuations go undetected[17]. However, this is critical for safe and timely adjustment of insulin administration and clinical decision making. Thus, there has been increasing interest in additional markers for better glycemic control over shorter timeframes. The markers in question, however, may have specific characteristics and are not equally suited for diabetes management.

Fasting glucose, postprandial glucose, and mean glucose

In contrast to HbA1c, estimation of glucose exposure for specific time periods overnight or 2 to 4 h postprandial may be useful in monitoring effects of food, exercise, or antidiabetic medications. Thus, fasting glucose (FPG) and postprandial glucose (PPG) provide an acute assessment of glycemia. However, in their original work on the relationship between FPG and PPG, Monnier *et al*[9] have shown that the relative contribution of these measures changes with increasing HbA1c values[3] and worsening of the metabolic situation is indicated by loss of postprandial glycemic control[18]. According to the ADA Standards of medical care in diabetes - 2014[19], FPG values of $\geq$ 7.0 mmol/L and 2-h plasma glucose (2hPG) of $\geq$ 11.1 mmol/L are considered criteria for the diagnosis of diabetes. Among a number of studies, which have examined the relationship of FPG or 2hPG to mortality, data from the Baltimore Longitudinal Study on Aging showed that FPG levels, exceeding 7.0 mmol/L increased the risk of mortality and the 2hPG added predictive power to that of FPG alone[20]. Impaired fasting glucose emerged also as independent predictor of cardiovascular mortality in the Australian Diabetes, Obesity and Lifestyle Study[21]. A recent meta-analysis suggested that reduction of FPG was related to a decrease of cardiovascular mortality with data on PPG pointing in the same direction[22].

Standl *et al*[23] have listed 14 long-term observational studies showing that elevated PPG levels increase the risk of cardiovascular disease or the occurrence of a cardiovascular event approximately threefold. By contrast, data from prospective studies on the association between PPG and cardiovascular risk in established diabetes are limited. The Diabetes Intervention study[24] has revealed the harmful link between PPG levels >10 mmol/L and increased risk of cardiovascular events and reported that reduction below this level decreased myocardial infarction and death in type 2 diabetes. Cavelot *et al*[25] confirmed this association in their follow-up study, demonstrating that PPG was a stronger predictor of cardiovascular

events than fasting glucose. Data obtained form a study conducted by Esposito *et al*[26] showed that postmeal incremental glucose values > 2.78 mmol/L, found in two thirds of study participants, were correlated with carotid intima-media thickness. Further support for the concept of treating elevated PPG came from a post-hoc analysis of the HEART2D study[27]. Although all these studies could not clarify, whether PPG is a real marker of cardiovascular events or a surrogate of complex metabolic processes taking place in the postprandial phase[28], this measure appears to be helpful for assessing the meal-induced glucose excursion and efficacy of diabetes treatment. In order to reduce the risk of cardiovascular events, the ADA[19] and IDF[29] recommend PPG values $\leq$ 10.0 and $\leq$ 9.0 mmol/L, respectively.

When considering glucose exposure, mean glucose is the metric with which the quality of diabetes management can be judged by clinicians as well as patients at shorter intervals and more easily than with HbA1c. For this reason, an expert panel of diabetes specialists recommended mean glucose/median glucose of all readings as one of the helpful glucose metrics[30].

Fructosamin and glycated serum proteins

In recent years, fructosamin and serum glycated proteins with shorter half-lives (14-21 and 17-20 d, respectively) than hemoglobin have been evaluated as markers of glycemia. Fructosamin is formed by attachment of the molecule primarily to albumin *via* a nonenzymatic reaction. The fructosamin assay uses a colorimetric method, is rapid, inexpensive and specific, and can be applied to measure glycation of serum proteins, principally albumin[31]; however, there is little standardization of this test. Several studies showed good correlations between fructosamin and HbA1c and glycated albumin[32]. Glycated albumin (GA) is a ketoamine that is formed *via* nonenzymatic glycation and has been reported to be a useful marker of shorter-term glycemic control in diabetes[33]. It is a more rapidly responding indicator than hemoglobin, although the glycation rate for both proteins is comparable[34]. Various methods to quantify GA are available but have not been consistently standardized-most common are affinity chromatography and enzymatic assays. Two cross-sectional studies, a Japanese and an American one, involving diabetic patients on hemodialysis[35,36], suggested that GA is a better marker of glycemic control than HbA1c. The consistent finding of significantly lower % GA/HbA1c ratios in diabetic patients without nephropathy compared to those on dialysis indicates that HbA1c underestimates glycemic control under these circumstances. It is likely that factors such as reduced survival of red blood cells and transfusions contribute to lowering of HbA1c levels in diabetic patients on hemodialysis. GA has been found useful in neonatal and gestational diabetes to detect short-term changes in glycemia[37,38]. Since glycated albumin was shown to be an independent variable of maximum glucose levels, it appears to be a more sensitive marker than HbA1c for glycemic excursions, as they occur during postprandial

times[39]. This is important because postprandial glucose excursions are known risk factors for diabetic micro- and macrovascular diabetes complications. More recently, it was found that serum GA levels are higher in relation to HbA1c in diabetes patients with reduced basal pancreatic β-cell function[40]. If in the state of postprandial hyperglycemia, indicating postprandial β-cell dysfunction, serum concentrations were found to be increased, then GA could be a useful surrogate marker for cardiovascular risk[41]. This has not yet been confirmed by clinical trials, although the finding of elevated GA, but not HbA1c levels in patient with coronary artery stenosis points out such a relationship[42].

1,5- Anhydroglucitol

Another analyte, 1,5-anhydroglucitol (1,5-AG), has been suggested for use as intermediate marker of glycemia to complement HbA1c measurements[43]. It is a naturally occurring inert polyol, which represents a six-carbon chain monosaccharide with a structure similar to glucose. An automated assay named GlycoMark™ is commercially available. 1,5-AG competes with glucose for tubular re-absorption and can hence not be used as a marker for glycemic control in patients with impaired kidney function. Furthermore, it should be noted that glucose levels exceeding the renal threshold for glycosuria, *i.e.,* 10 mmol/L (180 mg/dL), lead to a rapid reduction in serum concentration of 1,5-AG[44]. Poor glycemic control, indicated by high HbA1c values (> 9.0%, > 75 mmol/ mol), is therefore associated with lower not higher levels of 1,5-AG. Although this marker responds sensitively and rapidly to daily glucose excursions in patients with near or at goal HbA1c levels[45], it can not identify hypoglycemia. Dungan *et al*[46] have reported that 1,5-AG varied markedly in diabetes patients despite similar HbA1c and showed that this was mainly attributable to different postprandial glucose excursions. This makes 1,5-AG superior compared to HbA1c or GA (serum fructosamine) measurements as a marker for identifying postprandial hyperglycemia. Consequently, 1,5-AG has been used to evaluate drug strategies on postprandial glycemia. Studies, including exenatide[47], sitagliptin[48] or biphasic insulin[49], for example, support the usefulness of 1,5-AG as a marker to identify treatment effects on postprandial glycemic excursions that would have otherwise been missed. However, it must be emphasized that 1,5-AG is not able to determine glycemic variability.

Metrics of glycemic variability

Clinical observations in patients with type 1 and type 2 diabetes have revealed that glucose profiles can greatly differ even if patients are well-controlled. While in some patients small or moderate glucose excursions and rare hypoglycemia occur, there are marked postprandial increases with frequent hypoglycemic episodes in others. Such ups and downs in glucose levels over time, either measured within 24 h or from day to day at the same time point, reflect glycemic variability (GV) classified as within-day and between-day variability, respectively[50]. It was Monnier *et al*[51] who suggested that GV is one of the important components of dysglycemia in diabetes.

With the advent of CGM, quantification of GV gained considerable clinical importance[52]. Numerous indices for evaluation of various aspects of GV are currently available, which have been carefully characterized by Rodbard[53,54] and Cameron *et al*[55]. Although they can principally be calculated from frequently sampled SMBG data, *i.e.,* seven- or eight-point glucose profiles, it is advisable to use CGM datasets, because capturing relevant glucose peaks and nadirs requires sampling frequencies of 1-5 min. It is thus not unexpected that several studies found the magnitude of GV to depend on the sampling frequency[56,57]. Furthermore, it is very important to clearly differentiate between indices of GV and indices of the quality of glycemic control. Measures of GV quantify short-term changes in glycemia and reflect different and specific aspects of glycemic control but should not be interchanged. Validated indices such as mean amplitude of glycemic excursions (MAGE), mean of daily difference, continuous overall net glycemic action are often used in clinical research, but they are not easy to calculate. Several computer programs have recently been developed for better handling of sampled glucose data. We previously developed a computer program to calculate MAGE[58], and meanwhile, there is other software available, such as GlyCulator[59] and EasyGV (www.easygv.co.uk) for computing glycemic variability indices. In order to standardize measures of glycemia and glucose data reporting, an expert panel of diabetes specialists recommended for the ease of use, familiarity, and correlation with other factors of glycemic control, the following three measures of GV: SD around the mean glucose (SD), coefficient of variation (CV), and interquartile range (IQR)[30]. Especially, if CGM data are collected, IQR is the most reliable aggregate measure of GV, as the panel announced. Normative values for GV indices have been published by Hill *et al*[60] and Zhou *et al*[61].

In regard to the clinical relevance, it remains controversial whether GV is an independent causative or contributing factor to diabetes complications[62]. Nevertheless, there are a few studies in patients with type 1 diabetes to suggest GV to impact on the development of microvascular complications[63,64]. In an 11-year follow-up study, Bragd *et al*[65] found that GV measured by SD of blood glucose was a predictor of the prevalence of peripheral neuropathy. Moreover, Snell-Bergeron reported subclinical atherosclerosis to be associated with glucose levels and glucose SD in men with type 1 diabetes[66]. The potential importance of GV for the development of microvascular complications has been corroborated by Soupal *et al*[67] in a recent cross-sectional study of type 1 diabetes patients. This study showed significantly increased values for GV indices, such as SD, CV, and MAGE, for patients with microvascular complications as compared to those without complications. In this context, it should be

noted that analysis of data from the Diabetes Control and Complications Trial showed that long-term fluctuations in glycemia expressed as SDs of HbA1c independently relate to the development of retinopathy and nephropathy[68]. With respect to type 2 diabetes, there are more study data available than for type 1 diabetes, demonstrating close associations between GV and vascular complications[69]. In patients with well-controlled glycemia, Zhou *et al*[70] reported that increased MAGE is one of the risk factors for microalbuminuria. Vaduva *et al*[71] observed increased values for several GV indices in type 2 diabetic patients with chronic kidney disease compared to those without kidney damage; and Mirani *et al*[72] noticed glucose profiles with higher GV in insulin-treated diabetes patients on hemodialysis than in the hemodialysis-free intervals. One retrospective long-term follow-up study showed that fasting glucose variability was a risk factor for diabetic retinopathy independent of mean fasting glucose or HbA1c[73]. Regarding macrovascular complications, Chen *et al*[74] obtained data from a case-control study to suggest a significant association between GV and progression of atherosclerosis, as determined by measurement of carotid intima-media thickness. These latter data are consistent with the value of MAGE in predicting better than HbA1c major adverse cardiac events[75], coronary artery disease in newly diagnosed diabetes[76] and its severity in established type 2 diabetes[77]. A strong argument was presented for the role of GV by the recent analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial that revealed a clear association between SD of glucose and macro- as well as microvascular events in type 2 diabetes[78]. It should further be noted that MAGE, has been found by Rizzo *et al*[79] to be associated with impairment of cognitive function independent from the main markers of glycemia (HbA1c, FPG, PPG); and Penckofer *et al*[80] reported an impact of GV on mood and life quality in women with type 2 diabetes.

Finally, experimental findings and clinical observations suggesting that GV more than sustained chronic hyperglycemia induces increased oxidative stress[81] provide sure indications that GV is involved in the development of vascular disease. Because traditional measures of GV, with the exception of % CV, are closely correlated with mean glucose, it remains difficult to define an independent role for GV in the development of diabetes complications. Nevertheless, in clinical practice, minimizing GV is important to achieve acceptable glycemic stability without increasing the risk of hypoglycemia[82-84].

Metrics of glycemic risk

Essentially two indices, such as the average daily risk range (ADRR)[85] and the glycemic risk assessment diabetes equation (GRADE)[86] have been developed to grade the quality of glycemic control and to complement clinical assessment of diabetes treatment. These metrics are calculated by converting glucose values obtained from SMBG or CGM into risk scores, *i.e.,* they quantify the risk for glycemic extremes, both hyper- and hypoglycemia. They do not measure GV *per se*, rather its consequences. Nevertheless, ADRR scores correlate with several GV indices[60,87] and were further shown to correlate with patients' insulin sensitivity, epinephrine release[88], and weakly with basal β-cell function (HOMA%B)[89]. The ADRR includes the high blood glucose index and the low blood glucose index (LBGI), which quantify the risk for hyperglycemia and hypoglycemia. Among the advantages of ADRR that should be emphasized are the equal sensitivity to predict excessive hyperglycemic as well as hypoglycemic episodes and the possibility to use either SMBG or CGM data for its calculation[90]. On the other hand, ADRR has been considered as apparently less sensitive to therapeutic effects[87]. Nonetheless, with regard to our own research (Kohnert *et al,* unpublished data) we were able to differentiate between treatment modalities, as depicted in Figure 2. ADRR is usually reported as cutoff scores based on risk categories[90]. Even glucose meter software programs for automatic calculation are meanwhile available. Treatment studies that have used ADRR as outcome measure are still limited in number. Patton and coauthors[91] published a comprehensive review article on the use of ADRR in assessment research and treatment outcomes research, suggesting that adults and youths with diabetes could well benefit from monitoring their ADRR scores. However, as these authors stated, it is currently unknown to which extent ADRR is used in routine diabetes control.

GRADE has been introduced by Hill *et al*[86]. The GRADE score is an expression of the mean GRADE value derived from any glucose profile. The percentage of time spent in a specified range can be given as % GRADE$_{hypoglycemia}$, %GRADE$_{euglycemia}$, %GRADE$_{hyperglycemia}$. There have been only a few studies that have used GRADE scores, mainly in comparison with GV indices. One study has shown that GRADE was significantly improved in response to unmasking of CGM glucose values[87]; another study found GRADE scores to be reduced concomitant with lowering of GV after adjustment of therapy in patients with type 2 diabetes[84]. Although both ADRR and GRADE indicate increased glycemic risk, it should be noted that they are only moderately correlated with one another[87]. Nevertheless, as shown in Table 2, our data suggest that among the above metrics GRADE$_{hypoglycemia}$ and LBGI derived from CGM data are superior in estimating the risk of hypoglycemia (Kohnert *et al*, unpublished data).

Metrics of glucose dynamics

Regulation of glucose concentration is a complex process that is linked with several ultradian rhythms. Even though certain aspects of the failing glucoregulation observed in the development and progression of diabetes may be assessed by classical indices of GV, they do not include a time component[92]. The metrics of GV described above may thus give information about the extent of excursions, yet information about glucose dynamics is not

Table 2 Linear regression relating hypoglycemia as dependent variable with measures of glycemic control as independent variables in type 2 diabetes

Asymptomatic hypoglycemia	Measure	R^2	*P* value
Time (h/d) spent < 3.9 mmol/L	$GRADE_{HYPO}$	0.734	< 0.001
	LBGI	0.471	< 0.001
	% CV	0.293	< 0.001
	HbA1c	0.048	0.02

Data analyzed from 114 patients treated with diet and oral antidiabetic drugs. $GRADE_{HYPO}$: Glycemic risk assessment diabetes equation hypoglycemia; LBGI: Low blood glucose index; %CV: Percent coefficient of variation (Kohnert *et al*, Unpublished data).

Figure 2 Differentiation between treatment groups of type 2 diabetic patients using the average daily risk range scores. Sample size for each group is given in parenthesis. Between-treatment group differences were evaluated by one-way analysis of variance and are statistically significant (*P* < 0.001). MET: Metformin; SU: Sulfonylurea; OAD: Oral antidiabetic drugs; INS: Insulin (Kohnert *et al*, Unpublished data).

sufficiently provided, *i.e.*, how the glucoregulatory system moves from one state to another over time. In other words, GV indices are not suitable to gain deeper insight into regulatory dynamics. Various analytical methods have been used for indicating the range of glycemic dynamics in nondiabetic and diabetic patients associated with typical disease conditions. Time-series analysis techniques provide an approach to discover changes in glucose dynamics. Thus, autocorrelation function has been applied to glucose time series analysis in nondiabetic and type 1 diabetic individuals[93], but is difficult to exploit in type 2 diabetes due to the largely nonstationary data sequence. Utilizing detrended fluctuation analysis (DFA), Churruca *et al*[94] and Yamamoto *et al*[95] observed a loss of glucose profile complexity, as detected by the short- and long-term scaling exponent α1 and α2, in the progression from normoglycemia to impaired glucose tolerance to overt diabetes. Ogata *et al*[96] have reported that increasing long-range DFA scaling exponents reflect abnormalities in glycemic control. Interestingly, they found that the MAGE was correlated only to the DFA long-range scaling exponent α2 in patients with diabetes. According to Khovanova *et al*[97], glucose profile dynamics can be defined by three complementary characteristics: nonstationarity (DFA exponent α), linear predictability (autocorrelation coefficient γ), and amplitude of variation (SD of glucose). Kovatchev *et al*[98] and Molnár *et al*[99] introduced the Poincaré plot time series analysis tool to acquire temporal glycemic variability from CGM data. The primary method defines short-term and long-term variability, corresponding to the length of the minor SD1 and major SD2 axes of the plot. In his recent work, Crenier[100] extended Poincaré plot quantification by introducing and validating new partial Poincaré plot metrics, *e.g.*, area and shape of the fitting ellipse calculated at specific time points. While the majority of these metrics closely correlated with classical indices of GV, the shape index did not, indicating that the Poincaré plot captures many types of variability. One may speculate that in order to solve the question of whether GV is an independent contributor to the development of diabetes complications, analysis at multiple time scales would provide a better approach than use of classical indices. Indeed, in a recent cross-sectional, observational study,
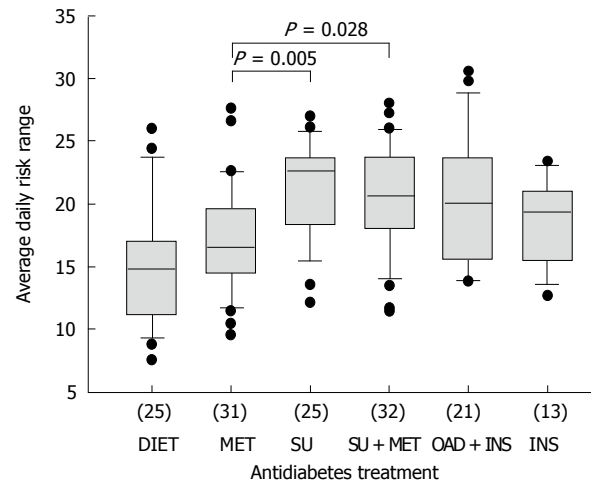
Cui *et al*[101] introduced Multi-Scale glycemic variability for analysis of CGM data at multiple time scales. They identified five unique ultradian GV cycles that modulate glucose over time ranges of 0.5 to 12 h and showed that greater GV within these cycles was associated with detrimental changes in brain morphology and function.

Biomarkers and surrogate biomarkers for diabetes complications
It is agreed upon that chronic sustained hyperglycemia represents one of the today's most important surrogate biomarker for development of microvascular diabetes complications. In addition to markers of glycemia, several novel biomarkers have been identified, capable of predicting onset or progression of nephropathy in type 2 diabetes. In a recent systematic review, Hellemons *et al*[102] assessed the validity of such biomarkers and found, for example, that serum interleukin 18, urinary ceruloplasmin, immunoglobulin G, and transferrin were valid markers to predict onset of diabetic nephropathy. Vascular cell adhesion molecule 1, interleukin 6, von Willebrand factor, and intercellular adhesion molecule 1 were identified as markers for progression of nephropathy. Although a number of circulating (*e.g.*, high sensitive C-reactive protein, brain natriuretic peptide), genetic, and imaging biomarkers (*e.g.*, carotid intima-media thickness) are significantly related with cardiovascular risk, their predictive power for individuals is restricted. The relationship of hyperglycemia with macrovascular disease is not as clear as with microvascular complications. Since large clinical trials[6,7] failed to provide convincing evidence that HbA1c is a reliable surrogate, adequate markers for cardiovascular outcomes in diabetic individuals with longer disease duration are not yet available[103]. The uncertainty related to cardiovascular
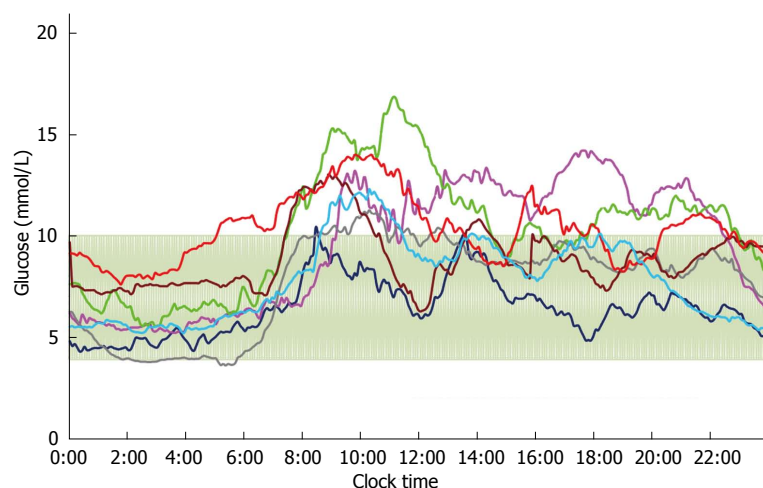
Figure 3 Continuous glucose monitoring traces from seven patients with an HbA1c value of 6.5% selected from the type 2 diabetes cohort treated with oral antidiabetes drugs. Average 24-h glucose profiles are shown. Shading indicates the glucose target range 3.9-10.0 mmol/L (modified from Kohnert *et al*, Bull Karaganda University 2013; 72: 6-15).

disease led to the release of the new recommendations on evaluating cardiovascular risk in drugs intended to treat type 2 diabetes[104] by the United Kingdom Food and Drug Administration. Given the complexity of diabetes, it is conceivable that no single biomarker can indicate the risk of complications or disease progression. New technologies, including metabolomics, proteomics, and genomics have the potential to unravel the pathogenesis of diabetes and put forward new concepts for the development of biomarkers beyond impaired glucose regulation.

GLUCOSE MONITORING

The development of hand-held blood glucose meters some decades ago made it possible for diabetes patients to monitor their own blood glucose levels at any time in a convenient way and enabled adjustment of therapy. With the universal availability of glucose meters, SMBG found broad application for management of glycemic control. However, this traditional monitoring usually measures single glucose values at a time point, which is determined by the user; it provides only a snapshot of the whole glucose picture and rapid changes occurring between single measurements escape detection. Introduction of the CGM technology presented a great step forward toward modern diabetes management, because it over comes limitations of traditional SMBG by producing glucose profiles instead of distinct measurements over several days, real-time glucose values, glucose trends and warnings when glucose values approach dangerously low or high levels. CGM recordings also provided evidence that diurnal glucose patterns may considerably differ in individual patients, even at identical HbA1c levels-a fact overlooked in the past. Figure 3 depicts individual average CGM profiles from a subsample of type 2 diabetes patients with identical HbA1c values. As can be seen, the profiles are quite different in that: (1) most of them exceed the target range (5%-23% glucose values above 10 mmol/L); (2) they show marked glycemic excursions (%CV 20.6-38.1); and (3) the glucose complexity long-range DFA scaling exponent α2 varies between 1.32

and 1.54. It is conceivable that frequent use of CGM and careful pattern analysis is able to improve glycemic control by uncovering such trouble points.

Clinical study outcomes and data obtained from every-day diabetes management have shown that the use of CGM can consistently improve glycemic control[105]. Notwithstanding that those with unstable diabetes who are prone to hypoglycemia and hypoglycemia unawareness will benefit most, the majority of diabetes patients can achieve their glucose targets when using CGM[106]. Two variants of CGM based on sensor technology are available: retrospective and real-time glucose monitoring[107,108]. While CGM systems such as CGMS Gold, Guardian T, Glucoday, and iPro2 were mainly designed as a tool for health care providers to collect glucose data over a sensing period of 3-7 d during which the data were masked to patients, provide real-time glucose monitors like Guardian RT, Dexcom Seven Plus, and Navigator real-time glucose values, trends, and alarms if glucose levels become high or low. The latter CGMs enable immediate therapeutic action, but require training experience for both health care practitioners and patients. However, all the above systems measure glucose subcutaneously, whereby the kinetics of the sensing process is defined by the physiology of the subcutaneous space. Glucose sensing in the peritoneal space, as recently shown, has the potential to optimize glucose monitoring because of faster intraperitoneal than subcutaneous kinetics[109].

Even though application of CGMs has convincingly demonstrated practical utility in diabetes management, *i.e.,* food response[110], reduction of glucose variability, time spent in hypo-/hyperglycemia, and improvement of HbA1c levels, this technology is still underutilized for a number of reasons[30]. One of the main problems is the lack of standardized metrics and a more user-friendly presentation of data. There are currently several well-established clinical and research measures that have shown to be useful in analyzing and characterizing CGM profiles. An expert panel of diabetes specialists identified time in range as one of the key metrics for guiding diabetes treatment[30]. This metric can be expressed either as "% of glucose readings" or "hours per day". As the
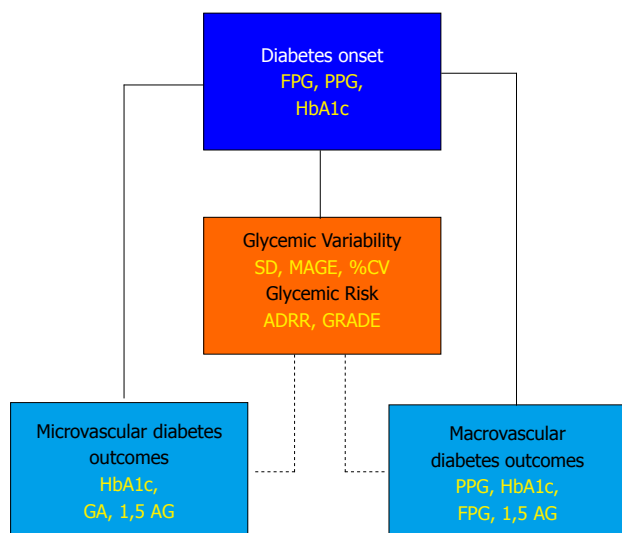
Figure 4 Glycemic Markers and Risk of Diabetic Complications. The solid lines show established relationships of the glycemic markers with microvascular and macrovascular diabetes complications; dotted lines represent possible relations with glycemic variability. FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; HbA1c: Hemoglobin A1c; GA: Glycated albumin; 1,5 AG: 1,5 Anhydroglucitol; SD: Standard deviation of plasma glucose values; MAGE: Mean amplitude of glycemic excursions; CV: Coefficient of variation; ADRR: Average daily risk range; GRADE: Glycemic risk assessment diabetes equation.

default target range, 3.9-10.0 mmol/L (70-180 mg/dL) was selected. Although this is not a "normal" range, it is commonly considered as acceptable in clinical practice. Individual targets closer to the physiological range can be defined, depending on age, comorbidities or patient compliance.

CONCLUSION

For the time being, HbA1c will remain the most important metric of long-term glycemic control, but may be supplanted by other parameters with advancing glucose monitoring technologies. Alternative metrics, such as GA and 1,5-AG can be clinically useful to assess medium- or short-term glycemic control, and in certain conditions that could interfere with HbA1c measurement. In view of the fact that many diabetes patients with apparently good glycemic control (HbA1c < 7%, < 53 mmol/mol) have high postmeal incremental glucose values, it seems warranted to integrate measurement of PPG into daily diabetes control. GV is one of the most important parameters that must not be neglected in order to optimize diabetes management. Since the known GV metrics are highly intercorrelated, any validated index can be used for evaluation of glucose fluctuations. MAGE and SD of glucose have been most commonly used; however, % CV is correlated to hypoglycemia and independent of mean glucose. ADRR as well as GRADE estimate the risk induced by high variability of glucose values and weigh low and high glucose equally. They can thus be helpful in patient care for assessments of glycemic quality. Based on our experience, we would recommend, in addition to the long-term measure HbA1c,

mean glucose and PPG as shorter-term indicators, and ADRR or GRADE for the quality of glycemic control. We would further recommend SD around the mean glucose, MAGE, and %CV as metrics of GV. Since these measures do not consider a time component Poincaré plot metrics might attract more attention to quantify short-and long-term GV and their relationship to the development of diabetes complications. For practical reasons and according to specific needs, a combination of shorter and longer term glycemic markers should be used for assessment of diabetes control to predict vascular outcomes more precisely. Finally, the control of glucose concentration is incomplete without dynamic measurements. Because of the limited available data, the utility of current metrics of glucose dynamics can not yet be judged, but they have shown promising potential to provide deeper insight into the glucoregulatory system hitherto not achieved with currently used metrics.

Since this article brings into focus metrics of glycemic control, the schematic representation in Figure 4 depicts which of these metrics may be predictive of micro- and macrovascular outcomes in diabetes. Nevertheless, it remains unclear whether glycemic variability and/or changes in glucose dynamics are implicated, but to achieve optimal glycemic control one should be aware that other factors than simply high blood glucose levels are likely to contribute to complications of diabetes. The discovery of new markers as reliable surrogates for clinical outcomes rather than simply glycemic control will advance the ability to assess the risk of complications and target treatment of diabetes.

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