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ORIGINAL ARTICLE

Prediction of the Risk to Develop Diabetes-Related Late Complications by Means of the Glucose Pentagon Model: Analysis of Data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study

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Abstract

Background:

By taking parameters into account that describe the variability of continuously monitored glucose and long-term metabolic control [hemoglobin A1c (HbA1c)], the glucose pentagon model (GPM) allows characterization of the glucose profile of individual patients with diabetes in a graphical format. A glycemic risk parameter (GRP) derived from this model might allow a better prognosis of the risk to develop diabetes-related complications than the HbA1c.

Methods:

To evaluate this hypothesis, we analyzed a subset of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring (CGM) study. The values of the different parameters that are integrated in the GPM were extracted automatically from CGM profiles registered before and after 6 months by means of the Medtronic CGM system in 108 patients.

Results:

In these patients, the significant reduction in HbA1c from 7.4% to 7.0% was accompanied by a reduction in glycemia from 164 to 156 mg/dl, standard deviation from 61 to 57 mg/dl, area under the curve >160 mg/dl 29.2 to 23.1, and time per day >160 mg/dl 634 to 576 min. This led to a subsequent reduction in GRP from 3.3 to 2.7; this decrease by 18.2% was significantly larger than that in HbA1c by 8.6% ($p < .001$). Changes in individual GPMs/GRPs support this observation. They also show the impact of high glycemic variability on GPM/GRP.

Conclusions:

Our analysis of data of a study with a considerable sample size and study duration showed that the GPM is not only helpful for rapid assessment of individual glycemic profiles and how therapeutic interventions influence these, but also appears to provide a better prognosis of the risk to develop late complications than the HbA1c *per se*. However, it is also clear that a true validation of such a model requires performance of a long-term study in a large number of patients with diabetes.

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Abbreviations: (AUC) area under the curve, (CIT) conventional insulin therapy, (DCCT) Diabetes Control and Complications Trial, (DRLC) diabetes-related late complications, (GPM) glucose pentagon model, (GRP) glycemic risk parameter, (GV) glycemic variability, (HbA1c) hemoglobin A1c, (JDRF) Juvenile Diabetes Research Foundation, (MDI) multiple daily injections, (SMBG) self-monitoring of blood glucose, (UKPDS) UK Prospective Diabetes Study

Keywords: continuous glucose monitoring, diabetes late complications, glycosylated hemoglobin, metabolic control, risk factors, risk prognosis

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Introduction

There is an ongoing discussion about the relevance of glycemic variability (GV) in the development of diabetes-related late complications (DRLC); however, at least experimental studies suggest that GV has relevance for the development of DRLC.[1–4] Also, clinical studies from the 1990s, such as the DECODE study,[5,6] the Diabetes Intervention study,[7] or the Kumamoto study,[8,9] suggest that, in patients with type 2 diabetes, there is a correlation between postprandial hyperglycemia and cardiovascular diseases.

Today, swings in glycemia of patients with diabetes can be fully documented by means of continuous glucose monitoring (CGM), something that is not possible by means of capillary self-monitoring of blood glucose (SMBG). Therefore, long-term studies with hard end points, such as the Diabetes Control and Complications Trial (DCCT) or UK Prospective Diabetes Study (UKPDS), do not allow firm statements about the impact of GV on the risk to develop DRLC. However, comparison of subgroups of patients with type 1 diabetes in the DCCT suggests that treatment with conventional insulin therapy (CIT; often associated with higher GV) or an intensified insulin therapy [multiple daily injections (MDI); i.e., lower GV] might induce a comparable metabolic control but that the risk to develop DRLC was different. Despite an equal hemoglobin A1c (HbA1c), the risk with MDI was only 40% compared with CIT.[10] Nevertheless, as stated earlier, such an analysis is not unambiguous proof that this difference was due to a difference in GV. These studies have proven that there is a close correlation of chronically elevated blood glucose levels (i.e., increased HbA1c levels) with an increased risk to develop DRLC.[11,12] Due to the fact that the HbA1c does not reflect GV, it might very well be that taking parameters into account that describe the glucose profile of individual patients to a larger extent might be of relevance for the risk to develop DRLC.

Based on such considerations, we developed the glucose pentagon model (GPM), in which, in addition to HbA1c, four additional parameters gained by analysis of CGM recordings are used: average glycemia, standard deviation of the glycemia, time per day during which glycemia was in the hyperglycemic range (>160 mg/dl), and area under the curve (AUC) for hyperglycemia.

Taken together, the selected parameters provide an integrated description of glycemia over the period of time under observation. These parameters also allow us to show other data indirectly, such as fasting glycemia, postprandial glycemic excursions, and mean amplitude of glycemic excursions, whereby the mean glucose concentration describes the average glycemic situation and the standard deviation describes GV to a certain degree.

Including the HbA1c, value in the glucose pentagon links the short-term parameters determined from glucose profiles with what is recognized as the best parameter for characterizing long-term metabolic control. It is true that, to a large extent, a linear correlation (r = 0.876) between the HbA1c value and the mean glycemic value determined from CGM entries does exist—at least with respect to the results of the A1c-Derived Average Glucose study.[13] As such, this value is theoretically already represented in the glucose pentagon. If the information provided by the mean glucose concentration is to be as meaningful as that yielded by the HbA1c value, however, the glucose profile must not contain any relatively long gaps over the 3-month time period under consideration. This has almost always been the case with day-to-day monitoring; however, at least up to now, this is why the HbA1c value was incorporated into the glucose pentagon. Another advantage of integrating the HbA1c value is that it provides a link to a verified laboratory diagnostic value covering a glycemic control in a time period of 8–10 weeks.

The time per day and AUC per day at blood glucose levels of >160 mg/dl are both parameters that characterize hyperglycemic periods over the course of a day and are considered to be additional risk parameters for developing diabetic complications. The AUC clearly correlates with oxidative stress and, as such, is relevant to the development of vascular complications.[14] These parameters are assigned their own independent significance, as both are only partially reflected in the calculated mean/standard deviation and the HbA1c. A value of 160 mg/dl is taken as the threshold value for physiological glycemia and thus increased risk. This value was selected because it represents a typical postprandial glucose maximum value for healthy individuals whose glucose profiles are recorded by means of CGM.[15] Time and AUC in the hypoglycemic range are not taken into consideration directly, however, as these do not correlate directly with the risk of developing diabetic complications.

Not directly related are the mean blood glucose and the AUC >160 mg/dl. Large swings in glycemia into very low and high extremes might result in similar mean values as is the case with much smaller swings; however, in the first case, AUC >160 mg/dl would be high, and in the second case, small. Also AUC and time >160 mg/dl are not directly correlated in all cases: the same AUC value can be the result of a high swing in glycemia for a short period of time or a small swing in glycemia for a long period of time. Therefore, we believe that both parameters are required to describe the glucose profile adequately.

The respective values of these parameters are entered in a diagram with one parameter given on one axis. Connecting the end points of these values result in an area with five corners, the glucose pentagon.[16] This graphical representation of these five parameters does not only enable a rapid visual analysis of the individual characteristics, but it also allows calculation of a "glycemic risk parameter" (GRP), which probably has a higher prognostic value for the development of DRLC as the HbA1c *per se*.[16] To obtain this GRP, the area of the pentagon obtained in patients with type 1 diabetes is divided by the area obtained in healthy subjects. Based on clinical data of patients with diabetes, a GRP of 1 corresponds to the risk of healthy subjects to develop DRLC; with a GRP of 1.5 to 2.0, the risk should still be very low; with 2.0 to 3.0, low; with 3.0 to 4.0, slightly increased; with 4.0 to 5.0, increased; with 5.0 to 7.0, high; and with >8.0, very high.

In an attempt to validate the assumptions behind the GPM/GRP, we analyzed a subset of the data collected during the Juvenile Diabetes Research Foundation (JDRF) CGM study; in this randomized, controlled, multicenter study, the benefits of CGM in patients with type 1 diabetes were evaluated.[17] We evaluated if changes in GRP are of better prognostic value to develop DRLC than the HbA1c *per se*.

Material and Methods

A total of 322 patients with type 1 diabetes participated in the randomized, controlled, multicenter JDRF study using three different CGM systems.[17,18] The patients were randomized into an intervention group and a control group. The JDRF provided us data from 108 patients (33.5% of study population), who used the Medtronic CGM system throughout the study, and were selected because one of authors of this article is an employee of Medtronic. The JDRF provided data only from that subset of patients who used the CGM system of Medtronic in this study. As stated earlier, the focus of this article is to evaluate if the analysis of a large CGM study by means of the GPM indicates advantages in comparison with the HbA1c as a risk parameter. In view of the relatively small sample size, we did not differentiate the subjects according to their age groups.

The CGM profiles of these patients were analyzed with software (see **Appendix**) that enables automatic extraction of the necessary data and subsequent generation of GPM graphs. At study start, patients recorded a glucose profile over 3 days using a "blinded" CGM device. After 6 months, CGM profiles were recorded again in an open manner. To generate the GPM, the HbA1c values measured at start and end of the study were used (see **Appendix**). From the area under the GPM, the GRPs were also calculated automatically. We did not differentiate the 108 patients according to their age, as this would have led to small patients groups.

The GRPs calculated for all patients at the start and the end of the study were subsequently analyzed for changes during the study, i.e., all individual changes were calculated, with a focus on shifts between GRP risk ranges (see Introduction). This observed change in the risk to develop DRLC was compared with the change in the risk indicated by the change in their HbA1c at begin and end of the 6-month period. This risk estimation is based on the results of the DCCT.[19] All calculations were made in Excel. Individual data were fitted to the different axis (best fit; see **Appendix**). The area of each pentagon is composed of the five triangles that are limited by the next axis. The total area of the GPM is the sum of these five triangles.

For statistical analysis of GRPs obtained at the start of the study with those at the end of the study in each patient, a paired *t*-test was used.

Results

In the JDRF study, use of a CGM system led to significant improvement in all parameters analyzed to characterize the glucose profiles of the 108 patients (**Table 1**). Subsequently, this led to an improvement in the individual GPMs and also in the GRPs by 18.2%; expressed in terms of risk classification, the average risk of patients to develop DRLC was reduced from slightly increased to low. A comparable analysis based on the HbA1c, averaged for all progression rates of the individual DRLC, showed a risk reduction of 5.4% only ($p < .001$), but the comparison of the number of patients

Table 1.
Changes in Parameters Characterizing Metabolic Control and Glucose Profiles Monitored by Means of a Continuous Glucose Monitoring System in 108 Patients Who Participated in the JDRF Study over a Period of 6 Months and the Glycemic Risk Parameter

	Start	End	*P*
HbA1c(%)	7.4 ± 0.9	7.0 ± 0.7	<0.001
Average glucose (mg/dl)	162.72 ± 33.48	156.24 ± 25.38	0.012
Standard deviation (mg/dl)	60.84 ± 16.56	56.52 ± 12.78	0.002
AUC >160 mg/dl (mg/dl/day)	29.70 ± 21.78	23.04 ± 16.20	<0.001
Time per day >160 mg/dl (min)	634 ± 288	576 ± 245	0.027
GRP	3.3 ± 1.4	2.7 ± 0.9	<0.001

in the different GRP risk ranges and how this is shifted during the study with that observed with HbA1c showed that the latter was less pronounced with the HbA1c (**Figure 1**).

Correlation between HbA1c and GRP values from the start of the study and after month 6 indicates two different groups of patients: a maximum regression of 0.83 was reached with a cutoff value of 3.5 for GRP in one group and of 0.58 in the patients > 3.5 (**Figure 2**).

Discussion

The observed change in the GRP in a considerable number of patients with type 1 diabetes during the 6-month period JDRF CGM study supports our assumption that taking parameters into account like GV, which further characterize the individual glycemic profile, led to a risk parameter that has a higher prognostic value to develop DRLC than the HbA1c *per se*. To illustrate this further, the observed changes in three individual cases are presented:

1. One patient (**Figure 3**, first row) with HbA1c of 7.6% at the start of the study (left column) showed a 77% decrease in his risk to develop DRLC during the study, induced by the improvements in glycemic control achieved. The relatively high GRP of 4.98 (i.e., borderline between average to increased risk), which was mainly induced by the high GV (i.e., high standard deviation values) at the start of the study, was decreased to 2.83 at the end. This led to a risk reduction by 43%, accompanied by a shift from the

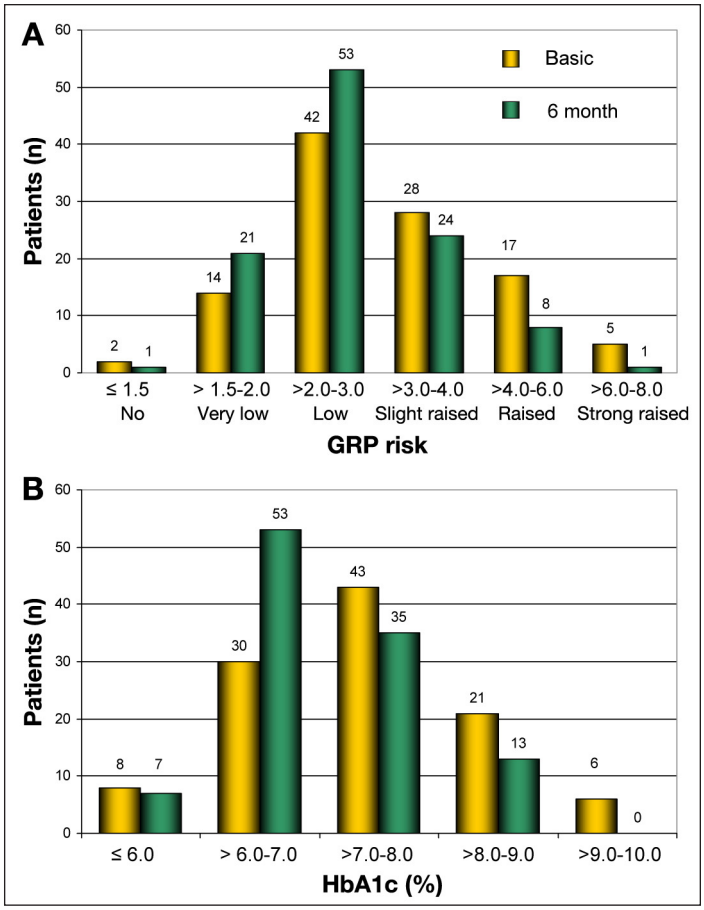

Figure 1. Change in the GRP **(A)** and HbA1c **(B)** within the JDRF study (values at basic evaluation and after 6 months).

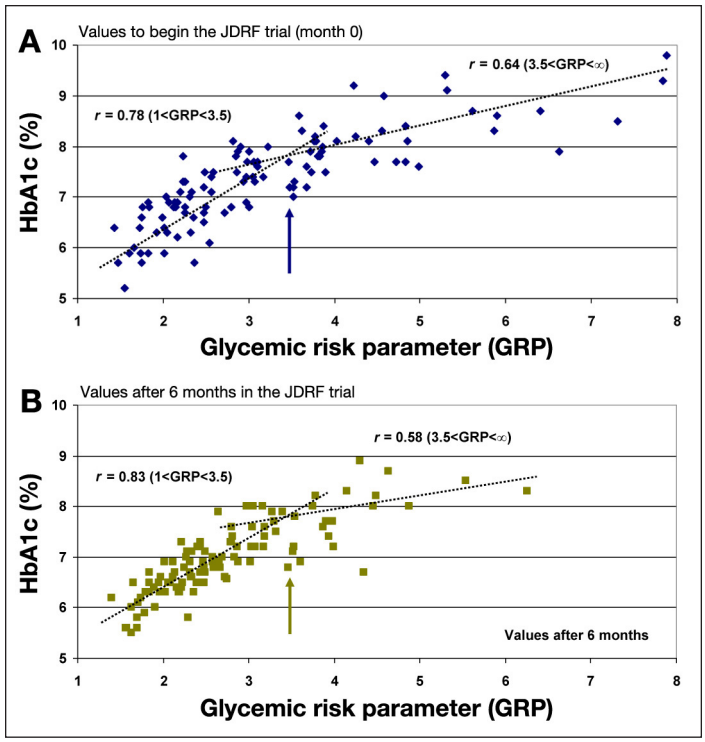

Figure 2. Correlation between HbA1c and GRP: data of 108 patients in the JDRF study at the **(A)** start of the study and **(B)** after 6 months.

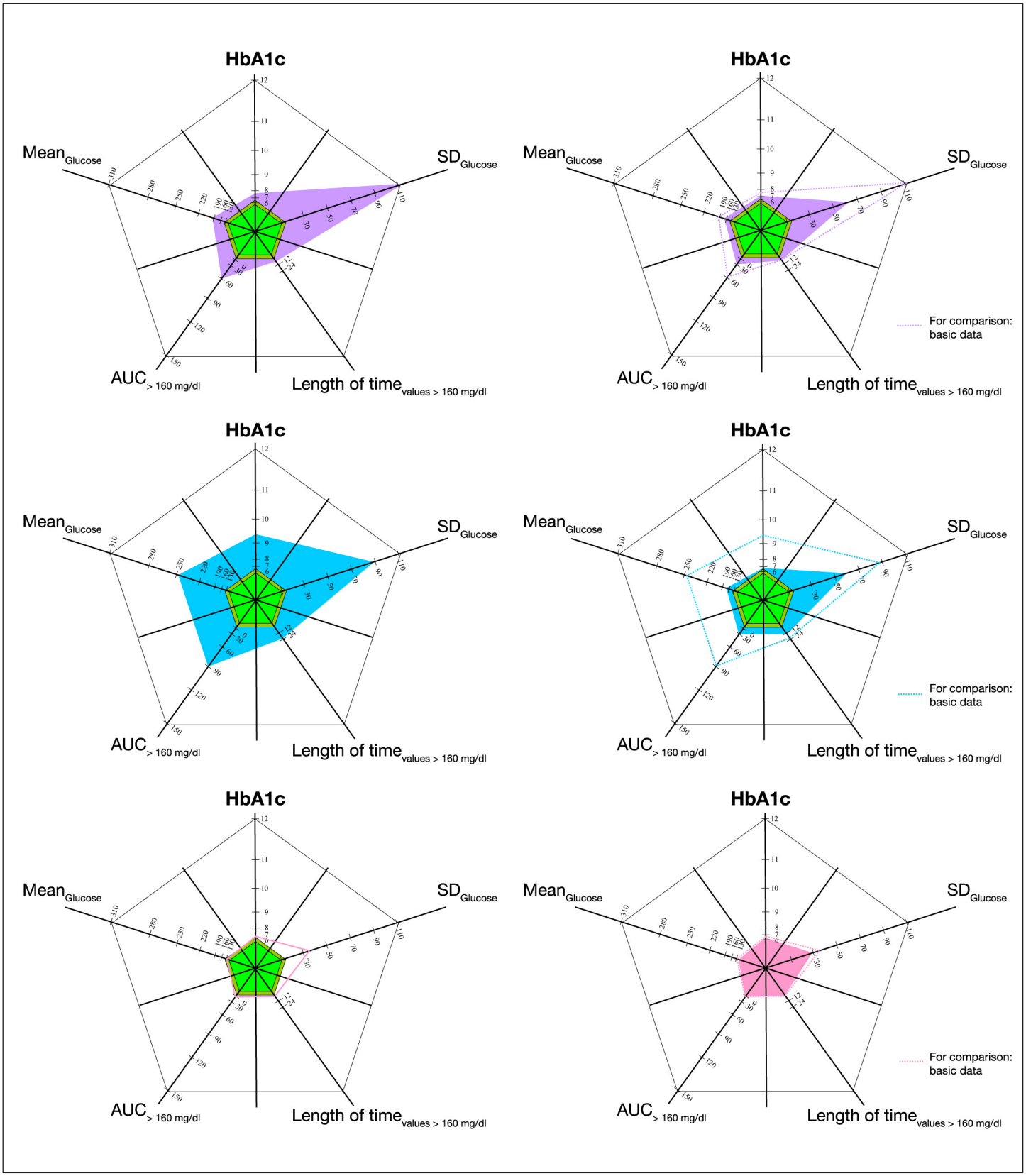

Figure 3. Glucose pentagons of three individual patients calculated by analyzing the CGM profiles recorded at the begin (left-hand column) and end of the study after 6 months (right-hand column): patient with high variability in glycemia (i.e., large standard deviation; upper row); patient with bad metabolic control (i.e., high parameters describing hyperglycemia; middle row); and patient with a close-to-normal metabolic control (lower row). SD, standard deviation.

GRP class with the average risk to the class with the low risk.

2. In another patient, the improvement in all glycemic parameters (**Figure 3**, middle row) led to a reduction in GRP from 7.83 (high risk) to 2.72 (low risk; risk reduction by 65.3%). This was induced by a decrease in HbA1c from 9.3% to 6.6%, combined with a risk reduction of 65.5%. In this patient, the AUC of the GPM at the study start was mainly driven by the parameters characterizing average glycemia (HbA1c, average glycemia) and hyperglycemia (AUC and time >160 mg/dl). After 6 months, the AUC depended more on the standard deviation of the glycemia (comparison of areas between adjacent axes: the proportion of the area with standard deviation axis is 73.7% of the total area). As shown in this example, a further improvement in metabolic control in such patients can best be achieved by a reduction in glucose swings by appropriate therapeutic interventions. A reduction in postprandial glycemic excursions by optimizing prandial insulin therapy and avoidance of hypoglycemia by usage of a CGM system are options to do so in clinical practice.

3. In a patient with good metabolic control (**Figure 3**, lower row; basal HbA1c 6.8%, i.e., risk increased by 30%) and a close to normal average glycemia, AUC and time in hyperglycemia had a low GRP of 1.76 already at the study start. During the JDRF study, the GRP further declined to 1.4, mainly driven by the improvement in HbA1c to 6.2%. An indication for the close correlation between the average glycemia estimated by CGM recording for some days and the HbA1c is that the line between the end point of the HbA1c axis and the average glycemia in both diagrams for this patient are parallel.

Our analysis of JDRF CGM study data indicates that the proposed glycemic risk parameter provides a useful index number describing the risk to develop DRLC. However, such an analysis is clearly not real proof. Such proof would require performance of a long-term clinical study with an appropriate study design/sample size. Performance of such a study would allow evaluating if this model/index provides a better prognostic reliability for the development of DRLC than the HbA1c *per se*. At the same time, other risk parameters proposed (such as the continuous overall net glycemic action, glucose lability index, glycemic risk assessment diabetes equation, and average daily risk range—which encompasses both the low and the high blood glucose indices) could be evaluated.[20–24] In principle, this would require a repeat of a study similiar to the DCCT. A study that is focused on cardiovascular end points would require inclusion of several hundred (if not thousands of) patients and a study duration of 4–5 years. Otherwise, the study would not have enough power to demonstrate a significant difference in hard end points, as the incidence of such events has drastically decreased. Patients in the intervention group would have to utilize CGM systems more or less continuously to monitor changes in GRP and adjust diabetes therapy. In the control group, the patients would perform SMBG only and would be informed about their HbA1c. If such a study would be organized and financed by an independent organization such as the JDRF, a high acceptance of the study results could be achieved. Without such a definitive study, all proposed index numbers/models will not become accepted, and we will have to continue to use the HbA1c as a risk prognosis parameter, being fully aware of the limitations of this parameter. Such a study would also allow taking other factors into account, such as age, duration of diabetes, frequency of hypoglycemia, lipids, and blood pressure. Also, the data collected in such a study would allow us to check whether certain levels of hyperglycemia (that we would select based on literature data) are optimal. It might be that taking other parameters into account, currently not included in the GPM, further increases the prognostic value of the GPM. Such a study would also allow us to evaluate if some parameters have more relevance than others, i.e., some should have more weight in a GPM than others. In its current version, all five parameters have the same weight.

The three cases presented earlier also illustrate how the GPM can provide helpful recommendations for changes in patient therapy that go beyond that of the HbA1c in daily practice. This approach allows us to monitor/visualize the prevailing hyperglycemia or swings in glycemia. Thus, graphical presentation of five parameters characterizing the CGM profiles of a given patient allows the treating physician to see which factors are relevant for improvement in glycemic control and to evaluate which changes in metabolic control take place once therapeutic interventions are made. Graphical presentation of CGM profiles in the format of GPM might be of special value in pregnant women with diabetes. In this patient group, it might also be possible to evaluate differences in the outcome of pregnancies in a controlled study.

In its current form, the GPM is designed for patients with type 1 diabetes; however, it can be adjusted easily

for patients with type 2 diabetes, taking data from the UKPDS study into account. If required, a version of the GPM can be developed (and validated) that describes not the general risk of developing DRLC, but the focus on individual DRLC like retinopathy, nephropathy, microalbuminuria, and neuropathy by taking the respective data of the DCCT into account.

Comparing information provided by HbA1c to that by GRP (**Figure 2**), the risk marker GRP increases in a linear manner with the HbA1c to a given extent but subsequently increases more rapidly than this, probably because of the growing influence of the GV and/or the AUC in the hyperglycemic region. We regard this as another hint that the HbA1c should not be used exclusively to quantify the quality of glycemic control.

In summary, analysis of data obtained in a 6-month randomized controlled trial demonstrates the capabilities of the GPM for daily practice and as a risk prognostic parameter in the treatment of patients with type 1 diabetes. Our evaluation suggests that the prognostic value of the GRP is higher than that of the HbA1c *per se*. In other words, taking factors such as GV also into consideration appears to provide a better prognostic value than the average glucose only. However, only well-designed long-term studies will allow definitive proof of the usefulness of this and similar models for risk prognosis in comparison with the HbA1c *per se*. Such studies should be performed by an independent institute (e.g., Jaeb Center, which also performed the JDRF study). Ideally, the study would be financed by an independent organization such as the JDRF to increase the acceptance of the study outcome by the academic community.

Disclosures:

Andreas Thomas is scientific manager of Medtronic, Business Area Diabetes, Germany.

Lutz Heinemann is a shareholder of the Profil Institut für Stoffwechselforschung, Neuss, Germany, and Profil Institute for Clinical Research, San Diego, CA. Lutz Heinemann is a consultant for a number of companies that are developing novel diagnostic and therapeutic options for diabetes therapy.

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Appendix

Calculation of the length of the five axes of the pentagons from the values of the parameters (best fit, data for patients with type 1 diabetes).

Parameter	Calculation of the length *Y* for each axis (mm)
HbA1c	$Y_{HbA1c}= [(HbA1c - 5.0) \times 1.22]^{2.0} + 14$
Average glucose	$Y_{AG} = [(AG - 90) \times 0.0217]^{2.63}+ 14$
Standard deviation	$Y_{SD} = (SD - 10) \times 0.6 + 14$
AUC > 160 mg/dl	$Y_{AUC} = (AUC \times 0.075)^{1.6} + 14$
t > 160 mg/dl	$Y_t = (t \times 0.00833) + 14$

The area of the pentagons is composed of five triangles, which are limited by the next axis:

$$AUC_{triangle} = ½ \sin 72^{o} \times Y_n \times Y_m = 0.4755 \times Y_n \times Y_m.$$

The total area of the glucose pentagon is the sum of the five triangles:

$$\text{AUC glucose pentagon: } A = \sum A_{triangle\ n.}$$

For the AUC of healthy subjects, a value of 466 mm^2 is obtained by using the length of the axis as defined in the fourth row of the table.