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# Continuous Subcutaneous Glucose Monitoring Shows a Close Correlation between Mean Glucose and Time Spent in Hyperglycemia and Hemoglobin A1c

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## Abstract

***Background:***

The Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study highlighted hemoglobin A1c (HbA1c) as the main predictor of diabetic complications. Currently, diabetes is managed by frequent capillary spot glucose measurements, but continuous monitoring systems may have the capacity of improving diabetic control. The SCGM 1 system is microdialysis based and allows for monitoring of changes in interstitial fluid glucose levels every minute. The aim of this study was to evaluate the correlation between HbA1c and short-term glucose excursions in patients with type 1 diabetes.

***Material and Methods:***

We investigated 91 patients with type 1 diabetes (mean ± standard deviation (SD); age 34 ± 10 years, body mass index 24.2 ± 4.1 kg/m$^2$) with a duration of diabetes of 17 ± 11 years for 4.8 ± 0.4 days. The average HbA1c was 7.9 ± 1.4%. From the monitoring profiles we determined individual mean glucose, the SD of glucose, and the relative time spent in hyperglycemia and hypoglycemia calculated as the area under the curve (AUC) with arbitrary cutoffs of 180 and 70 mg/dl, respectively.

***Results:***

Mean glucose, SD glucose, and hyperglycemic and hypoglycemic AUC all correlated with HbA1c, but with decreasing statistical power. In multiple linear regression analysis, mean glucose was the sole independent variable ($r$ = 0.626, $p$ < 0.0001). A close correlation between HbA1c and various measures of short-term hyperglycemic values was observed. There was a close correlation between mean glucose and SD glucose, pointing toward increased variability with increasing mean glucose.

*continued* →

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**Abbreviations:** (AUC) area under the curve, (BMI) body mass index, (CGM) continuous glucose monitoring, (DCCT) Diabetes Control and Complications Trial, (HbA1c) hemoglobin A1c, (MARE) mean absolute relative error, (PG) plasma glucose, (PRESS) predictive error sums of squares, (SD) standard deviation

**Keywords:** continuous glucose monitoring, HbA1c, metabolic control, microdialysis

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**Abstract cont.**

***Conclusion:***

Mean glucose generated after short-term continuous monitoring is the main predictor of HbA1c and reveals increased lability of glucose with increasing mean glucose and HbA1c.

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## Introduction

Long-term follow-up studies have increased the awareness of the need for normalization of glycemia in patients with diabetes. Such trials have shown normalization of hemoglobin A1c (HbA1c) as a key parameter in metabolic control in diabetes to prevent or delay development of late complications. In order to keep HbA1c within normal range, most patients resort to frequent self-monitoring of blood glucose, which can lead to an acceptable degree of glycemia.[1] Although HbA1c provides insight into glycemia over the last 3 months, it has yet to be clarified which element has the larger impact on glycosylation of hemoglobin—time spent hyperglycemic or amplitude of excursions. It can be speculated that both time and amplitude have an impact on glycosylation, as clinicians are confronted with patients exhibiting vast diurnal glucose oscillations as well as patients with seemingly stable elevated glycemic levels, with both patient groups displaying poor long-term regulation in terms of HbA1c. However, two studies using self-monitoring of blood glucose failed to show an impact of glycemic lability on HbA1c when controlling for mean glycemia.[2,3] Others have suggested that postprandial glucose excursions contribute to a relatively large extent in well-controlled patients, whereas fasting glucose levels contribute more in poorly controlled patients.[4]

The recent development of continuous glucose monitoring (CGM) devices such as the CGMS,™ DexCom,™ Guardian RT,™ and GlucoDay™ has enabled a change of scope from focusing not only on long-term metabolic control, but on gaining insight in glucose profiles during shorter time periods. The current systems are able to analyze glucose excursions minute by minute, thereby providing the means for intensified monitoring of short-term metabolic control.

Currently, the components determining the actual level of HbA1c are poorly understood. It is known that the level of HbA1c reflects the level of glycemia during the preceding 2–3 months due to the average life span of circulating erythrocytes of 120 days. However, recent plasma glucose (PG) levels (1–4 weeks earlier) contributes more than PG levels prevailing more than 60 days earlier,[5] resulting in HbA1c as a "weighted average" of the level of glycemia during the last 120 days. It is not clear whether fasting PG or postprandial PG contributes primarily in the glycation of hemoglobin. One study showed that postlunch PG was a better predictor than fasting PG.[6] In line with this, a reappraisal of data from the Diabetes Control and Complications Trial (DCCT) showed that postlunch (and bedtime) PG levels were good predictors of average HbA1c, whereas fasting PG tended to underestimate HbA1c, especially at high levels of HbA1c. The same study showed that postbreakfast PG markedly overestimated HbA1c.[7] In children, mean values of glucose obtained during CGM correlated to HbA1c, with no influence of pre- or postprandial glucose levels in multiple regression analyses; at the same time, a marked day-to-day variability in glycemia was found.[8]

The aim of the present study was to evaluate the perspectives of CGM in the clinically important setting of shortening the interval of decision making in diabetes. Thus, we evaluated the predictive value of 4 to 5 days of CGM in patients with type 1 diabetes with the SCGM 1 system for metabolic control as assessed by the measurement of HbA1c. Specifically, we analyzed the impact of mean glycemia, hyper- and hypoglycemic episodes, and the variability in glucose levels on HbA1c.

## Materials and Methods

The study was conducted at two centers (Medical Department M, Aarhus University Hospital and Profil Institute for Metabolic Research, Neuss) participating in the clinical *in vivo* development phase of the SCGM 1 system (Roche Diagnostics, Mannheim, Germany).

We enrolled 91 patients [age mean ± standard deviation (SD): 34 ± 10 years] with type 1 diabetes. The data sets of these patients were collected from a larger population of more than 200 series based on the following criteria: (1) sufficient technical quality of the measurements and (2) elimination of artifacts studying all readings manually. For each experiment, the first 12 hours of the up to 5-day recordings were omitted from analysis in order to avoid any run-in phase calibration problems, as the microdialysis system applied uses a slow flow rate as well as dry catheters, which prolongs the equilibration with the interstitial tissue. At the end of each experiment, the last half hour of *in vivo* measurement was also discarded to avoid the inclusion of data derived after the explantation of the catheter. Subsequently, the membrane was placed in glucose of a known concentration, and repeated calibration procedures were performed to assess the individual lag time of each catheter.[9]

Patients who participated in the experiment at the two clinics were recruited from their outpatients. During the clinical experiment the patients kept up their normal therapy, thus a variety of all types of insulin were used in the study group. In order to maintain their normal treatment they were allowed to self-adjust in the same amount they habitually did in their own home based on their own spot measurements. They were not given access to CGM data nor protocol-obtained glucose measurements. Meals were given at standardized times. Patients were encouraged to upkeep their normal physical activity level, such as using an exercise bike or walking in the clinical ward. Furthermore, they were encouraged to perform the same amount of activities on all study days.

All patients received written and oral information according to the Declaration of Helsinki II and signed consent forms. The study was approved by the local ethical committees of the centers participating in the study and was performed according to Good Clinical Practice Guidelines.

### *SCGM 1 System*

The SCGM 1 system consists of a sensor unit device and a belt-held sensor containing the microdialysis system. The system allows for up to 120 hours of dialysate glucose measurements every minute. Data are stored by custom-designed software—online display of dialysate glucose is transferred wirelessly from the sensor unit to the portable data manager where additional information (insulin administration, meals, exercise, etc.) can be entered as separate events in the data managing device.

The sensor unit uses a roller pump that provides a push–pull flow resulting in a perfusion of the microdialysis membrane with 0.3 µl/min. The perfusion fluid (Ringer chloride, $Na^+$147 mmol/liter; $K^+$ 1.4 mmol/liter; $Ca^{2+}$ 2.3 mmol/liter; $Cl^-$ 156 mmol/liter, pH 6; osmolality 290 mosmol/kg) passes through the catheter, achieving approximately 95% equilibration with the interstitial fluid.[10] Glucose oxidase is mixed with the dialysate and passes the *ex vivo* sensor, creating a current in the nanoampere range. The current is averaged over 60 seconds, and data are stored in the sensor unit and the data manager.

### *Study Procedure*

The microdialysis probe is inserted into the subcutaneous abdominal adipose tissue after skin puncture with a 16-gauge needle.

In order to calibrate the obtained dialysate glucose values to capillary blood glucose, spot measurements were performed up to 20 times per day with a built-in blood glucose meter as described later. Based on the spot measurements performed throughout the experiment and the lag time-corrected (inherent physical microdialysis lag time of 31 minutes) corresponding interstitial values, a linear regression approach was used in order to calibrate the system. This approach was chosen by the manufacturer at the current system development stage in order to evaluate the optimal performance of the system.[11]

The sensor versus reference measurement performance was evaluated by calculating the mean absolute relative error (MARE) and the percentage of predictive error sums of squares (PRESS). MARE reflects lag time-corrected glucose values measured by the SCGM 1 and reference values obtained by capillary blood glucose measurements. %PRESS expresses the percentage of residual values throughout the study and calculated as described previously.[12] Clarke error grid analysis was performed, and results were presented for zones A through E as well as for the clinically acceptable zones A+B.[13]

### *Assays*

Hemoglobin A1c was measured by high-performance liquid chromatography at both sites (normal range 4.8–6.2). Spot measurements of capillary blood glucose were performed by the glucose oxidase method on a Glucotrend™ blood monitoring glucose device (Roche Diagnostics, Mannheim, Germany).

### *Statistical Analysis*

Time spent in hyper- or hypoglycemia was expressed as the duration above and below a certain threshold; 180 and 70 mg/dl were used as cutoff values. Area under the curve (AUC) during hyper- or hypoglycemia was calculated applying the trapezoidal method and was seen in relation to AUC of normoglycemia.[14] Glucose values were found to be distributed normally. On this background, mean and SD of glucose were calculated for the entire glucose profile. The SD of individual patients was seen as an index of the stableness of glycemia, i.e., the higher the SD, the more labile the diabetes of a given patient was considered. Pearson's correlation analysis was made to analyze relations between time spent in hyper- or hypoglycemia and HbA1c. Stepwise linear regression was used to test the combined influence of time spent in hyper- or hypoglycemia, and SD on HbA1c. The Kolmogorov–Smirnov test of normal distribution of data was performed and, depending on this, a parametric (Student's $t$ test for paired samples) or nonparametric (Wilcoxon signed ranks test) test was used. $P$ values $< 0.05$ were considered significant. Nonparametric data were presented by median and range, whereas parametric data were displayed as mean ± SD. SPSS 13.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

## Results

The insertion of the microdialysis catheters was well tolerated by all patients. No adverse events were observed apart from minor bleeding upon insertion. Carrying the SCGM 1 for the duration of the study period was well tolerated by participants. The body mass index (BMI; 24.2 ± 4.1 kg/m$^2$) was within normal limits but with a wide range, hence body composition varied considerably. We studied 38 females and 53 males. Patients had diabetes for a considerable and variable length of time (17 ± 11 years). HbA1c was 7.9 ± 1.4%.

Mean glucose level and the SD of glucose correlated closely with HbA1c **(Figure 1)**. The patients were studied for 84 ± 15 hours during which time spent in hyperglycemia accounted for 20 ± 16% (range 1–99%). The fraction of time spent in hyperglycemia also correlated closely to HbA1c ($r$ = 0.595, $p < 0.0005$) **(Figure 2A)**. We also pooled the total time spent outside normal glycemia (time spent in hyperglycemia and time spent in hypoglycemia) and looked at correlation with HbA1c; however, this led to a weaker correlation. Changing the cutoff level to 160, 170, or 190 mg/dl did not change this correlation materially (results not shown). The average fraction of time spent in hypoglycemia was 8 ± 2% (range 0–7%). There was a weak negative correlation between HbA1c and relative time spent in hypoglycemia **(Figure 2B)**. There was a tight correlation between mean glucose and the standard deviation of glucose during the study period **(Figure 3)**, pointing toward increased glucose excursions with an elevated mean glucose. There was no significant correlation between HbA1c or mean glucose and age, BMI, or diabetes length. We then analyzed the correlation between the different measures of short-term glycemia and HbA1c and showed that as the observation period was extended from 1 to 5 days, the correlation between the different measures of short-term glycemia and HbA1c got stronger **(Table 1)**.

Multiple regression analysis, with HbA1c as the dependent variable and mean glucose, SD, time spent in hyperglycemia, and BMI as independent variables,

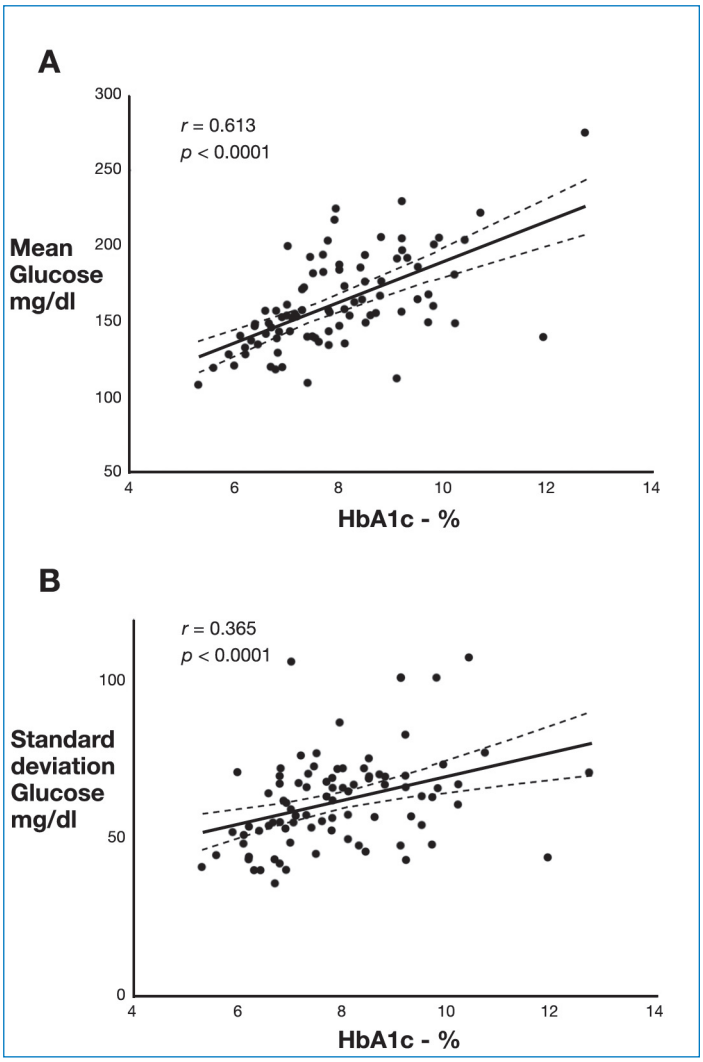


**Figure 1.** Correlation between HbA1c and mean glucose of the registered glucose profiles (A) and the standard deviation of glucose (B). The regression line is indicated by a solid line, and the 95% confidence interval is indicated by dashed lines. The regression coefficient and significance level are shown.

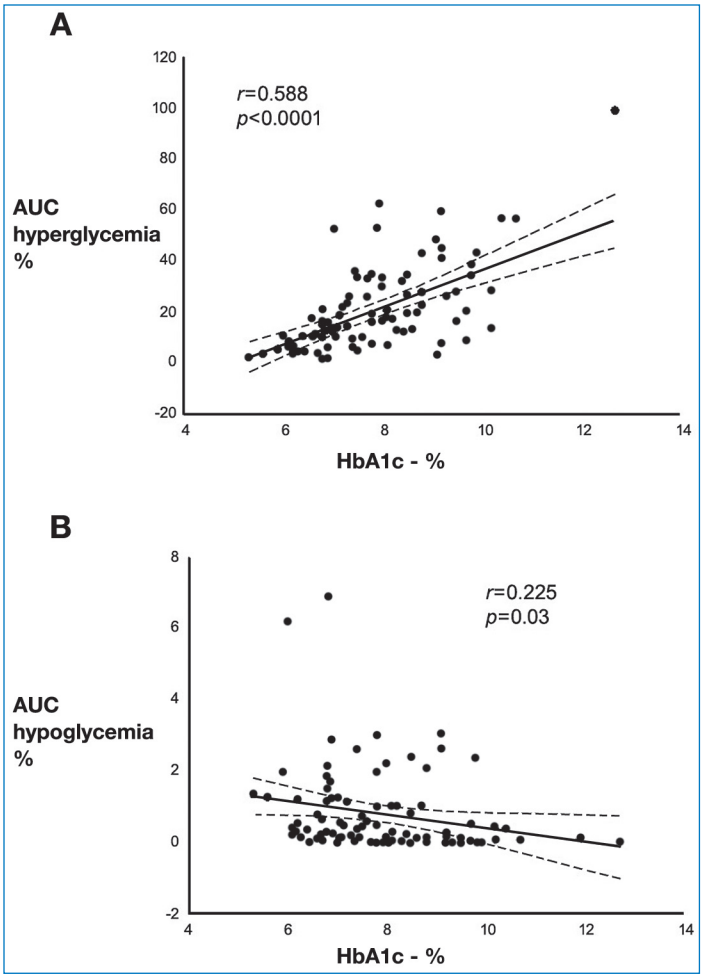


**Figure 2.** Correlation between HbA1c and AUC of hyperglycemia given as a fraction of the total observation time above a threshold of 180 mg/dl (A) and AUC of hypoglycemia given as a fraction of the total observation time below a threshold of 70 mg/dl (B). The regression line is indicated by a solid line, and the 95% confidence interval is indicated by dashed lines. The regression coefficient and significance level are shown.

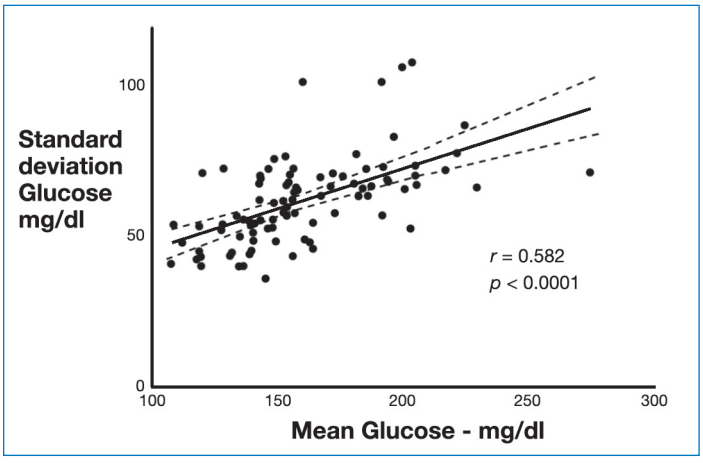


**Figure 3.** Correlation between mean glucose and the standard deviation of glucose. The regression line is indicated by a solid line, and the 95% confidence interval is indicated by dashed lines. The regression coefficient and significance level are shown.

**Table 1.**
**Correlation between HbA1c and Different Measures Derived from Continuous Subcutaneous Glucose Monitoring[a]**

| | Correlation coefficient, *r* | | *p* value, day 1 | *p* value, day 5 |
|---|---|---|---|---|
| | Day 1 | Days 1–5 | | |
| Mean glucose | 0.49 | 0.63 | <0.0001 | <0.0001 |
| Relative AUC of hypoglycemia | -0.14 | -0.22 | 0.2 | 0.03 |
| Relative AUC of hyperglycemia | 0.43 | 0.58 | <0.0001 | <0.0001 |

[a]Data were analyzed after the first full day of data sampling and then the following days (data not shown for days 2, 3, and 4).

showed that the only glucose-derived variable retained in the model was mean glucose. Surprisingly, BMI was a significant contributor as well ($r$ = 0.660, $p$ < 0.0001). This analysis was performed even though some of the variables (i.e., glucose-derived variables) were closely related; as such, colinearity was a potential problem.

The overall system performance was excellent as described by MARE [10.6 (5.8–53.0)] and %PRESS [11.9 (7.1–50.6)] values. Clarke error grid analysis showed that almost all (e.g., >98%) of the measurements were in the clinically acceptable A and B zones (median % [min;max] ($N$ number of measurements): A 88 [9;100] ($N$ = 8465); B 12 [0;74] ($N$ = 2791; A+B 100 [39;100] ($N$ = 11184); C 0 [0;27] ($N$ = 19); D 0 [0;24] ($N$ = 62); E 0 [0;9] ($N$ = 5)).

## Discussion

The main finding of this study was the tight correlation between mean glucose measured during a short period of time with the long-term measure of average glycemia, HbA1c. We also found a close correlation between time spent during hyperglycemia (here chosen arbitrarily as a cutoff of 180 mg/dl) and HbA1c. Results indicated that mean glucose during a short period of time spent during hyperglycemia may explain around 60% of the variation in the level of HbA1c. This explanatory level should be considered in the light of the study period being merely 84 hours, whereas the time span covered by a single HbA1c measure was approximately 120 days (2880 hours).

Correlation analyses showed that a number of characteristics derived from CGM data are closely related to HbA1c. The design of the study does not consolidate whether this relation is a consequence of the fact that

CMG-recorded data are representative of longer term metabolic control in the body or whether the short-term fluctuations themselves are correlated to HbA1c. Although all these measures of course are interrelated, they still illustrate different aspects of what we perceive as glucose control. It is interesting that the higher the mean glucose level, the higher the standard deviation of glucose. Derr and colleagues[3] also found a correlation between glycemic variability and HbA1c, but after adjusting for the mean glucose level in a linear regression model, this effect lost significance. As also shown, when performing multiple regression analysis, the only glucose-related variable retained in such a model was the mean glucose level. Surprisingly, and not easily explained, BMI was also an explanatory variable in such a model, although with only marginal influence. The close relationship between short-term mean glucose and HbA1c was also described in a study using a CGM system in diabetic patients and frequent spot measurements in nondiabetic individuals.[15] These authors described a very close relationship, especially in diabetic patients, but somewhat poorer in nondiabetic individuals, as also found previously.[16] In an analysis of data from the DCCT study, a tight and linear relationship was also found between an average of 18 corresponding individual seven-point profiles and HbA1c measurements in a large study group. Studying the relationship between pre- or postmeal glucose and HbA1c showed a poorer correlation.[7] In an attempt to further the understanding of what mainly contributes to a given level of HbA1c, quintiles of HbA1c (6.5–11.3%) were studied and related to fasting and postprandial hyperglycemia, evaluated after four-point spot measurements.[4] The authors found a progressive shift in the contributions of fasting and postprandial hyperglycemia, with fasting hyperglycemia gaining increasing importance in poorly controlled diabetes.[4] In a study conducted with a CGM system, a correlation was found to exist between HbA1c and various AUC measures in a pediatric population, although the relationship was not present when glucose fell below 90 mg/dl.[8] The authors did not find a correlation to postprandial glucose values, but only to the total AUC.

The use of HbA1c for evaluation of long-term metabolic control of patients with type 1 and 2 diabetes is based on the results of two large trials, the DCCT and United Kingdom Prospective Diabetes Study, showing that increased levels of HbA1c were associated with an increased frequency of diabetic complications. The tight correlation found here between mean glucose and time spent in hyperglycemia and HbA1c suggests that both fasting and postprandial glucose values contribute to a given HbA1c value. Modern diabetes therapy aims for near-normal levels of blood glucose to avoid elevated levels of glucose, which is known to increase the risk of complications in both type 117 and type 2 diabetes.[18] To maintain a normal level of glucose it is necessary to have knowledge of the variations in glycemia seen in nondiabetic individuals during daily life, and data from a CGM system could therefore be an important adjunct to clinical decision making.

The level of system error obtained in this study is acceptable, with most values falling in the clinically acceptable regions when performing Clarke error grid analysis. Once we had included a data set, no selection was made based on the quality of data obtained with the CGM system. The MARE value is comparable to values reported in the literature with other continuous glucose monitoring devices.

Some of the CGM techniques are based on microdialysis, which allows analysis of interstitial analytes in various tissues. The technique involves the perfusion of a catheter with a semipermeable membrane and the recovery of the analyte of interest across the membrane into the dialysate. The application of microdialysis in continuous glucose monitoring has been performed in various setups during the last decade. The inherent problem with the microdialysis approach has been the need for off-line analysis of the dialysate. This issue has been addressed in publications utilizing microdialysis in continuous monitoring.[19,20] The SCGM 1 uses an in-line glucose oxidase sensor, which in turn implies the introduction of a lag time. We have assessed the lag time with the current system, which is around 30 minutes. With CGM systems, 24-hour surveillance of glycemia is possible. The devices are typically inserted in adipose tissue and can be left for several days, with reliable measurements of glucose every 1–5 minutes.[11,12] However, the interpretation of such data sets containing up to 1440 daily measurements of glucose is not straightforward, especially without knowledge of the variation in nondiabetic individuals. In any given individual it is necessary to have information not only of insulin dose and type, but also of daily life pattern, sleep, food intake, exercise, etc. It still remains to be proven whether use of a CGM system can improve glycemic stability and thus decrease HbA1c,[1] although one randomized study showed that the use of a CGM system decreased the duration of hypoglycemic episodes, without decreasing HbA1c.[21]

In short, we have shown that short-term CGM-generated mean glucose, SD of glucose, and time spent during hyperglycemia correlate with HbA1c, with the greatest contribution stemming from mean glucose levels.

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**Disclosures:**

Hereby we, Claus H. Gravholt, Jannik K. Nielsen, and Christian B. Djurhuus, confirm that we, as physicians, have performed the present study regarding continuous glucose monitoring and that we have received an unrestricted research grant from Roche Diagnostics. Roche Diagnostics is currently developing continuous glucose monitoring devices for commercial purposes.

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