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Continuous Glucose Monitoring

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PATIENT BACKGROUND

36 years old, Type 1 diabetes for 16 years. HbA_1c consistently below 6.0%. Checks blood glucose 6-8 times/day. On MDI with 26 units of longer-acting insulin in a.m. and a mixture of R/Humalog® with meals and snacks. Patient reluctant to loosen control or lower insulin dosage despite several severe episodes of hypoglycemia. Additional insight needed.

INSIGHT INTO THE PROBLEM

First tracing—72-hour period

- *Sensor average: 85 +/- 29 mg/dl*
- *Sensor range: 40-187 mg/dl*
- *Multiple daily episodes of blood glucose less than 50 mg/dl, asymptomatic*

RECOMMENDATIONS

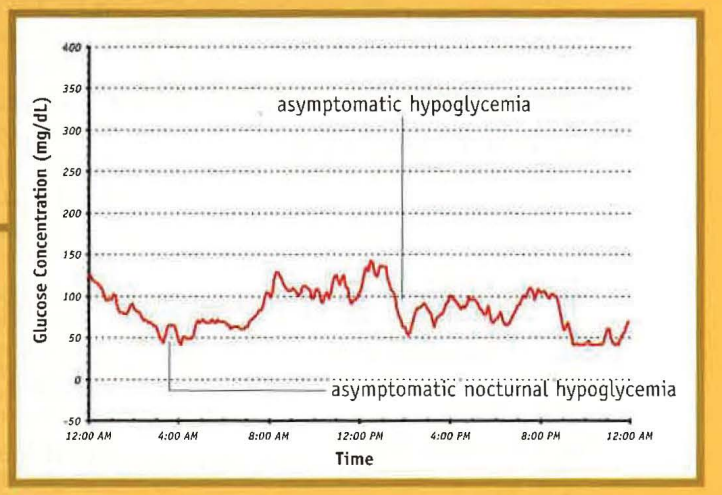
Reduce insulin by 10-20%. Patient agrees after seeing results.

RESULTS OF THERAPY CHANGE

Second tracing—72-hour period at 3-month follow up

- *Sensor average: 116 +/- 44 mg/dl*
- *Sensor range: 40-284 mg/dl*
- *Prolonged nocturnal hypoglycemia eliminated*
- *Marked reduction in overall hypoglycemia*
- *Insight leads to improved level of control*

Glucose Sensor Profile First Tracing



Glucose Sensor Profile Second Tracing

Case study submitted by Chris Sadler, PA-C, CDE, Diabetes and Endocrine Associates, La Jolla, CA

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Diabetes Technology & Therapeutics

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Symposium Paper

Continuous Glucose Monitoring with Glucose Sensors: Calibration and Assessment Criteria

VOLKER LODWIG, Ph.D.,[1] and LUTZ HEINEMANN, Ph.D.[2]
ON BEHALF OF THE GLUCOSE MONITORING STUDY GROUP

ABSTRACT

Continuous glucose monitoring (CM) by means of minimally invasive or noninvasive glucose sensors can help to further optimize metabolic control in patients with diabetes without need for frequent capillary blood glucose measurements. Most glucose sensors measure glucose concentration in the interstitial fluid (ISF). Because of the varying conditions in this compartment, a general in vitro calibration (= factory calibration) by the manufacturer appears not to be possible. Therefore, calibration of the sensor signal must be performed by the patient himself repeatedly. The calibration procedure can be performed by means of conventional capillary blood glucose measurements in order to transform the sensor signals obtained from the specific compartment (e.g., ISF) into "blood" glucose values. A number of aspects can influence the validity of this procedure. The relationship between changes in blood glucose and in ISF glucose, in both time and concentration dimensions, is not well understood, especially during dynamic changes. The physical lag time, which critically depends on the glucose sensor technology used, can also introduce a systematic calibration error. After the first calibration, usually performed some hours after the application of a given glucose sensor, recalibration at certain intervals is necessary. Therefore, patients should critically assess the values displayed by a CM system. In the case of implausible glucose values they should verify the results by means of a conventional capillary glucose measurement. Up to now there is no consensus on assessment criteria to be used for evaluation of CM system performance and calibration quality. Existing methods of displaying CM values against corresponding reference values, including linear regression analysis and error grid analysis, as well as numeric criteria such as System Error, Predicted Error Sum of Squares (in %), and Mean Absolute Deviation are not generally applicable to CM. It appears as if they do not allow sufficient description of data obtained with CM systems. There is a pressing need to develop novel adequate assessment criteria enabling a better characterization of CM system performance. If these were used uniformly by all manufacturers and scientists assessing CM systems, this would allow a fair comparison of the performance of different systems.

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The members of the Glucose Monitoring Study Group are: Jens Sandahl Christiansen, Hans Orskov (Aarhus, Denmark); Theodor Koschinsky (Düsseldorf, Germany); Thomas Pieber (Graz, Austria); Adelbert J.M. Schoonen (Groningen, The Netherlands); Volker Lodwig (Mannheim, Germany); Lutz Heinemann (Neuss, Germany); Urban Ungerstedt (Stockholm, Sweden); and Cornelia Haug (Ulm, Germany).

INTRODUCTION

With the currently available diagnostic and therapeutic measures, intensified insulin therapy is the most effective treatment of patients with diabetes mellitus. A cornerstone of intensified insulin therapy is preprandial capillary blood glucose measurement. However, this is an inconvenient, cumbersome, and painful procedure, and this limits further intensification of blood glucose monitoring. Continuous glucose monitoring (CM) by means of minimally invasive or noninvasive glucose sensors can help to overcome this hurdle and further optimize metabolic control.

Conventional blood glucose meters are calibrated by the manufacturer (i.e., the measured signal is converted by a factory-determined function into a glucose reading). Subsequently patients have only to check the quality of their measurements at certain intervals using a control solution of known glucose concentration.

Minimally invasive glucose sensors are permanently in contact with the compartment, usually interstitial fluid (ISF), where the glucose concentration is being measured. Because of the considerable variation in local conditions, a general in vitro calibration by the manufacturer appears not to be possible. Therefore, glucose sensors require calibration by the patient several times per day by means of a conventional capillary blood glucose measurement. Thereby, the values measured by the CM system in a specific body compartment (e.g., ISF) are transformed into "blood" glucose values.

This prompts the critical question: Does this calibration step lead to a measurement with an acceptable precision and accuracy, especially over longer periods of time? In order to describe the quality with which the continuous monitoring is performed, certain assessment criteria must be evaluated.

MINIMALLY INVASIVE VERSUS NONINVASIVE

Some minimally invasive glucose sensors measure ISF glucose concentration directly inside the human body by breaching the skin barrier, but not entering blood vessels. With other minimally invasive approaches the sensor is placed outside the body, to which ISF or an extract from the ISF is transferred by microdialysis, microperfusion, or iontophoresis, or through micropores. Most sensors use the enzyme glucose oxidase (GOD) for specific glucose measurement.

Noninvasive glucose sensors measure glucose concentration in the skin (and underlying tissues) without breaching the skin barrier. Most of these sensors use nonspecific measurement of glucose, and consequently the quality of the measurement can be insufficient. For a detailed overview of the different sensor technologies under development see Koschinsky and Heinemann.[1]

CALIBRATION: GENERAL ASPECTS

The definition of calibration, as given in the Webster dictionary, is: "standardizing by determining the deviation from a standard so as to ascertain the proper correction factors." For most CM systems, calibration means transformation of the electrical signal generated by the glucose sensor (a current, in nA) into a blood glucose-related signal by a measurement of a capillary blood sample using a conventional glucose meter (in mmol/L or mg/dL). This allows calculation of a calibration factor or function. Applying this factor or function to the sensor signal converts this into the desired calibrated "blood glucose readings."

By means of this procedure, the calibrated sensor values should match the actual blood glucose levels. However, a considerable number of factors can affect the validity of this assumption (see below).

When evaluating the metabolic status of a given patient in a clinical situation, his glucose history (profile) has to be assessable by the treating physician on demand. Depending on the decision of his treating physician the individual patient can get on-line access to his data. This requires a retrospective calibration of the recorded data. This approach has also proved to be useful in the evaluation of the performance and quality of CM systems during clinical development. In contrast, for everyday use in patients with diabetes a real-time display of

the current glucose levels is necessary (i.e., on-line systems). For such approaches only prospective calibration is of relevance.

PRECONDITION FOR CALIBRATION

For adequate calibration of CM systems, the following preconditions should be fulfilled:

- The blood glucose measurement used for calibration is reliable (i.e., the blood glucose meter has a high accuracy and precision) and delivers a value close to the "true" glucose concentration (in general the risk of outliers should be reduced by double measurements of the same capillary blood sample).
- With capillary blood glucose measurement and a sensor signal origin from ISF, the glucose concentrations are measured in different compartments. Therefore, the correlation between glucose changes in one compartment with the subsequent one in the other compartment should be high.
- The corresponding measurements made by both methods in the different compartments should refer to the same point in time.

Calibration of CM systems demonstrates some peculiarities and deviations from these ideal conditions, with a potentially negative impact on the quality of the calibrated data. Until now, the influence of these shortcomings has not been completely elucidated and must be subject to further investigations.

Common methods and criteria for assessment of calibration quality, as used for example routinely in the clinical laboratory or for assessment of blood glucose meters, are not generally applicable to continuous glucose monitoring. Thus, new methods and criteria must be developed specifically adapted to the requirements of CM systems.

CHOICE OF REFERENCE METHOD

Commonly, reference methods in clinical chemistry are the most precise, most accurate, and highly sophisticated and require well-trained personnel. Because the patients have no permanent access to a clinical laboratory, a surrogate method has to be used instead: the capillary blood glucose measurement. This method is easy to perform and user-friendly. Therefore, use of a conventional blood glucose meter is considered to be the "reference" method of choice.

However, the reliability of such measurements is not optimal. Because of the great improvements over the last decades, the analytical performance of blood glucose meters is approaching clinical laboratory standards nowadays. Apart from the inaccuracy and imprecision of the device, preanalytical errors can also occur, depending to a large extent on the skills of the patient and his compliance with the instructions given. These problems can be reduced in part by performing duplicate measurements one immediately after the other from the same finger prick.

CORRELATION BETWEEN BLOOD AND ISF

The calibration relies to a considerable extent on a strong correlation between the glucose levels in blood and subcutaneous ISF. Otherwise, a systematic error will be inherent in the sensor signal, with potentially serious consequences. Depending on the technique used, the absolute glucose levels in the subcutaneous ISF were reported to be 50–100% of that in the blood.[2,3] In the majority of the publications about this matter a close correlation between glucose levels in blood and subcutaneous ISF is reported. However, most of these investigations were performed under steady-state conditions only, meaning with slow changes in blood glucose (<1 mg/dL/min). Nevertheless, in the daily life of patients with diabetes, more rapid changes in blood glucose also occur (14 mg/dL/min). There is a significant lack of knowledge regarding the exact correlation between blood and subcutaneous ISF glucose during dynamic changes, in both the time and the concentration dimension (see below). In humans, the extent of intra- and interindividual variability of that correlation has not been investigated so far. The correlation between capillary blood glucose and intradermal ISF is also a matter of debate.

COMPARTMENTS AND PHYSIOLOGICAL LAG TIME

Although there is a free and rapid exchange of glucose between plasma and ISF, a change in blood glucose level will not immediately be accompanied by an identical change of the ISF glucose level under dynamic conditions. There is a so-called physiological lag time, which can, according to the published data, vary from seconds up to several minutes.[3,4] This lag time can affect calibration when a blood glucose measurement is performed during a phase with rapid changes in blood glucose, probably resulting in a certain mismatch between the glucose values measured in the two compartments. This mismatch may result in an erroneous value in the concentration domain and/or the time domain. A calibration based on such a mismatch might be dangerous for the patient, if blood glucose levels are declining towards hypoglycemic values.[5]

It is probable that the relationship between ISF and blood glucose is influenced by the prevailing plasma insulin levels. Whether or not the relationship between blood and ISF glucose is linear over the full glucose concentration range observed in humans is not known. If not, more complex calibration functions for different blood glucose ranges must be applied.

In summary, a calibration should be performed only at times when the correlation between blood and ISF glucose concentrations is considered to be stable and differences are most probably minimal. Theoretically, performing the calibration process during dynamic situations (e.g., after meals) should be avoided. Probably the time prior to a meal is most suitable; however, this remains to be determined in appropriately designed studies.

PHYSICAL LAG TIME

A substantial physical lag time may occur between sampling and subsequent glucose measurement, depending on the glucose monitoring approach utilized. This lag time is longer with glucose monitoring systems in which a glucose-containing fluid is transferred to an extracorporeal sensor for glucose measurement (i.e., microperfusion-, microdialysis-, and iontophoresis-based systems). Some sensors can also have a remarkable physical lag time due to the time required for diffusion of glucose through the layers that cover glucose electrodes in order to improve biocompatibility. With other types of sensors a "physical" (mathematical) delay can occur due to the algorithms used for computation of the data.

If the calibration measurement is inadequately synchronized with the sensor signal, a systematic error may be introduced. In order to optimize the timing of the calibration and to avoid data entry errors, some CM systems are in development that have built-in blood glucose meters (e.g., the SCGM1 System) that automatically link the result of the capillary blood glucose measurement with the corresponding sensor signal.

A known and constant physical delay can, to a certain degree, be compensated for by the appropriate mathematical tools, extrapolating with a given degree of certainty into the near future. This is, because of its variability, not possible in the case of the physiological lag time. In summary, it must be taken into account that glucose concentrations measured in blood at a certain point in time do not necessarily match the glucose concentrations measured by the sensor at the same point in time in another compartment (e.g., ISF).

RETROSPECTIVE CALIBRATION

Using the method of minimizing squared errors, a data set can be calibrated over all capillary blood glucose measurements performed. This procedure defines the accuracy of the sensor measurements, while the precision is given by the calibration. An underlying drift must be compensated for by introducing an additional parameter in order to have the best precision. By means of such a calibration "overall," accommodating both variation and drift, each glucose profile can be retrospectively well described. This holds true for all CM systems.

PROSPECTIVE CALIBRATION

Depending on the relationship between glucose concentration and sensor signal, different

types of calibrations can be applied. If there is a specific relationship between the sensor signal and the glucose concentration and no other factors have an effect on the signal (e.g., factors resulting in a drift over time) or the signal is adjusted for factors having an effect on it (e.g., temperature), a single blood glucose measurement may be sufficient to calibrate the system (one-point calibration). If a linear relationship shows a substantial intercept but unknown intercept (i.e., a sensor signal in absence of glucose), at least a two-point calibration is necessary, comprising measurements at two different glucose levels (e.g., prior and after meal intake). In the event of the sensor signal showing a linear drift (= change of sensor sensitivity over time), at least a two-point calibration should be performed at two different time points. Nonlinear relationships would require multipoint calibration.

Mathematically, linear calibration can be described by the following two equations:

$y = ax + b$ (drift-free glucose sensor system)

$y = (ax) + ct + b$ (glucose sensor system with drift)

where y is the reference blood glucose value; x is the sensor current; a, the calibration factor, can be determined by minimizing squared errors (calibration overall) or by the slope of the calibration curve (one-point calibration); b, the intercept, can be defined during manufacturing; and c, the time-dependent factor, can be determined by regression analysis (calibration overall) or by slope differences (multipoint calibration).

RUN-IN PHASE AND RECALIBRATION

A newly applied glucose sensor requires time for the signal to stabilize; this is because of the interaction of the sensor with its biological surroundings and, in the case of minimally invasive sensors, the impact on the sensor signal of local wound reaction and wound healing. The "break-in time" can vary from hours to days, depending on the specific technology utilized. During this period sensor signal changes do not correspond to real changes in glucose concentration (i.e., meaningful calibration of the signal is not possible). Because of possible intra- and interindividual variability in the duration of this break-in time, a conservative approach must be taken to ensure the calibration is successful. In other words, the (first) calibration should only be performed once the period of sensor signal instability is definitively over.

Assuming the local conditions stabilize, theoretically, no further calibrations are necessary. However, if the sensor sensitivity changes over time, probably because of insufficient biocompatibility (that is to say "sensor fouling"), unreliable glucose concentration values may possibly be obtained, and system recalibration is required. The lack of long-term stability of the sensor signal has proved a major problem for many types of CM sensors (i.e., they show a decrease in sensitivity to glucose with time, which suggests a decline of the glucose profile that is, in fact, not real).[6] The underlying reasons for the change in sensitivity are (complex) interactions between body fluids and the sensor surface, which becomes coated with proteins and other substances as well as a physiological reaction to the foreign body (i.e., inflammation). In addition, a decline in the activity of the enzyme used for glucose sensing can take place.

Recalibration of the CM system at certain time intervals is mandatory with most types of sensor, as it is virtually impossible to predict the drift of the sensor signal. The frequency with which such a recalibration is necessary varies greatly (e.g., glucose electrodes require several calibrations per day, whereas other CM systems require only one calibration daily). For each glucose monitoring system the optimal frequency of recalibration points has to be evaluated. In the case of (virtually) drift-free systems (e.g., those based on microdialysis technique), recalibration at longer intervals might be possible.

PRACTICAL ASPECTS OF THE CALIBRATION PROCEDURE

It is evident that the required frequency and the ease of the calibration procedure will sub-

stantially contribute to the acceptance of a CM system by the patients. In addition, adequate training in the calibration procedures should be provided to patients, physicians, and other health care professionals. All must be aware that incorrect calibration will introduce a systematic error into the measuring process of a given on-line CM system, resulting in unreliable blood glucose profiles and potentially exposing the patient to a substantial risk.

Since studies on calibration procedures are usually performed under controlled clinical-experimental conditions, they do not reflect the patients' everyday life. One can foresee situations in everyday life that will cause calibration to fail. Due to the probable lifelong use of CM systems and the high user numbers, there is a high probability that such issues will occur. Therefore, patients should be encouraged to assess critically the results displayed by any CM system and relate them to their individual situation in order to check plausibility. This requires sound knowledge both about diabetes and of the individual sensor properties. Consequently, patients will need to undergo intensive training and education.

Situations requiring immediate therapeutic decisions and active responses often occur during, or as a result of, dynamic metabolic changes. Consequently, given the above, in the event of extremely pathological or implausible glucose values, the glucose concentrations displayed on the CM system should be verified, by measuring capillary blood glucose concentration with a conventional blood glucose meter, prior to any therapeutic decision being taken. This will reduce any potential risk to the patient.

SELECTION OF CALIBRATION POINTS

The importance of choosing the "right" calibration point and its impact on all subsequent "blood" glucose sensor values can be demonstrated using a sample data set (Fig. 1), which displays the results of CM over 4 days. The data were obtained from a 47-year-old patient with type 1 diabetes during the clinical development of the SCGM1 System (Roche Diagnostics GmbH, Mannheim, Germany), a microdialysis-based CM system. In order to evaluate the quality of the calibration, the relative differences (in percentages) between the sensor signal and the corresponding capillary blood glucose measurements were determined for all subsequent measurements and plotted over time (Fig. 2).

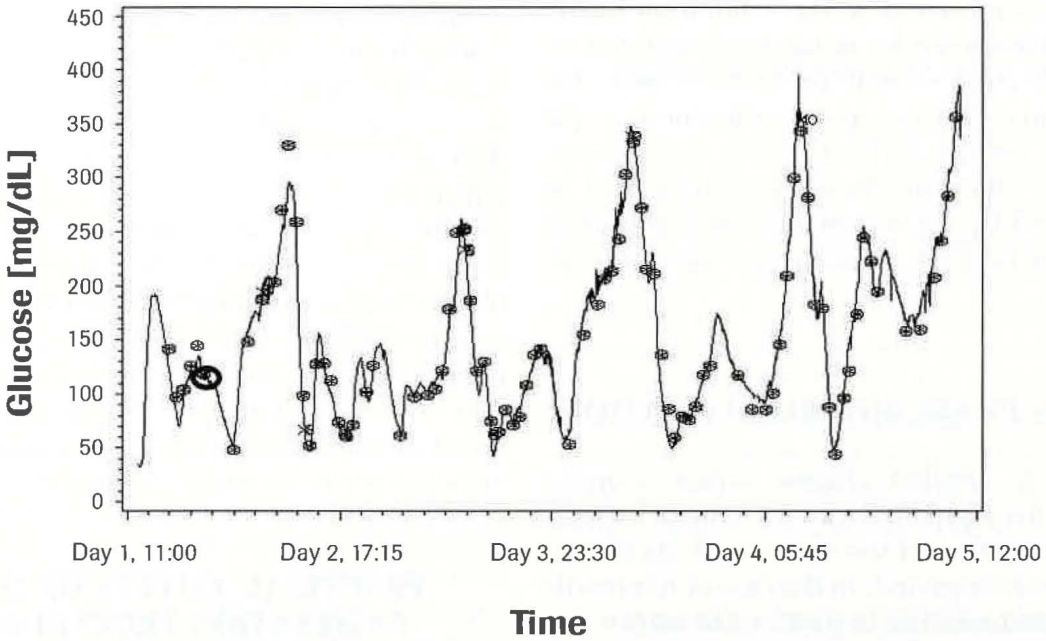

FIG. 1. CM over 4 days. The line represents the sensor signal (SCGM1 System); the asterisks indicate blood glucose reference measurements [identical to those from the Accu-Chek® Active (Roche Diagnostics) glucose meter]. The reference value used for calibration is circled.

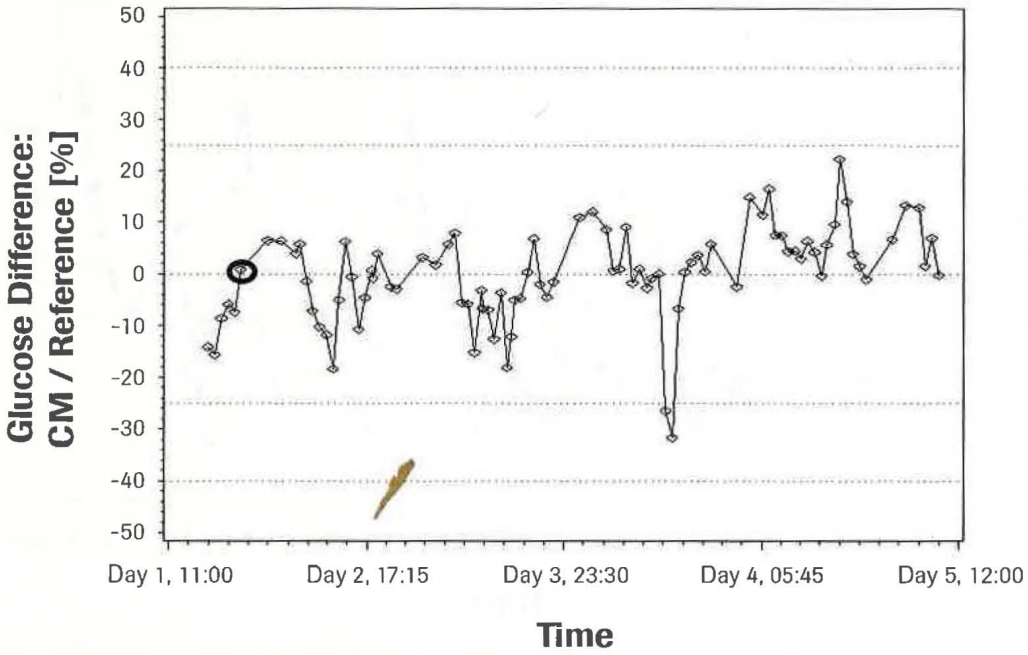

FIG. 2. Differences between sensor and reference measurements versus time. The calibration point is circled.

By definition the calibration point lies on the zero line (no difference between sensor signal and capillary blood glucose measurement), and all following sensor measurements differ more or less from the corresponding capillary blood glucose values (according to the precision and the accuracy of the system). However, the differences fluctuate around the zero line, showing excursions within a range of ±25% (except two outliers on Day 3), suggesting that a sufficiently reliable glucose monitoring can be achieved over several days by a single one-

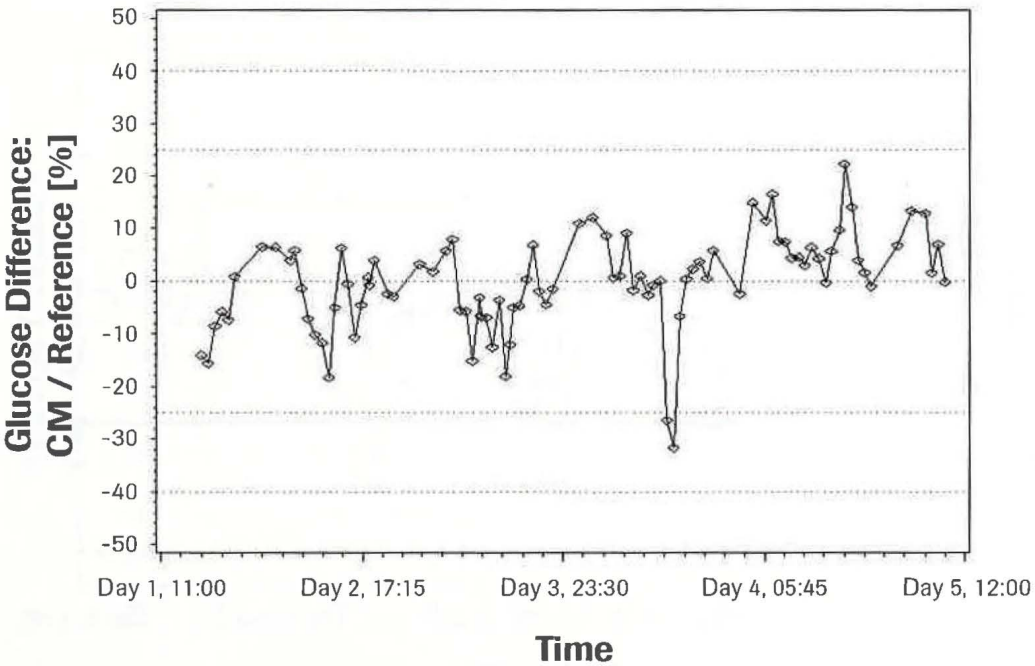

FIG. 3. Differences between sensor and reference measurements versus time. Calibration was performed taking all data points into account.

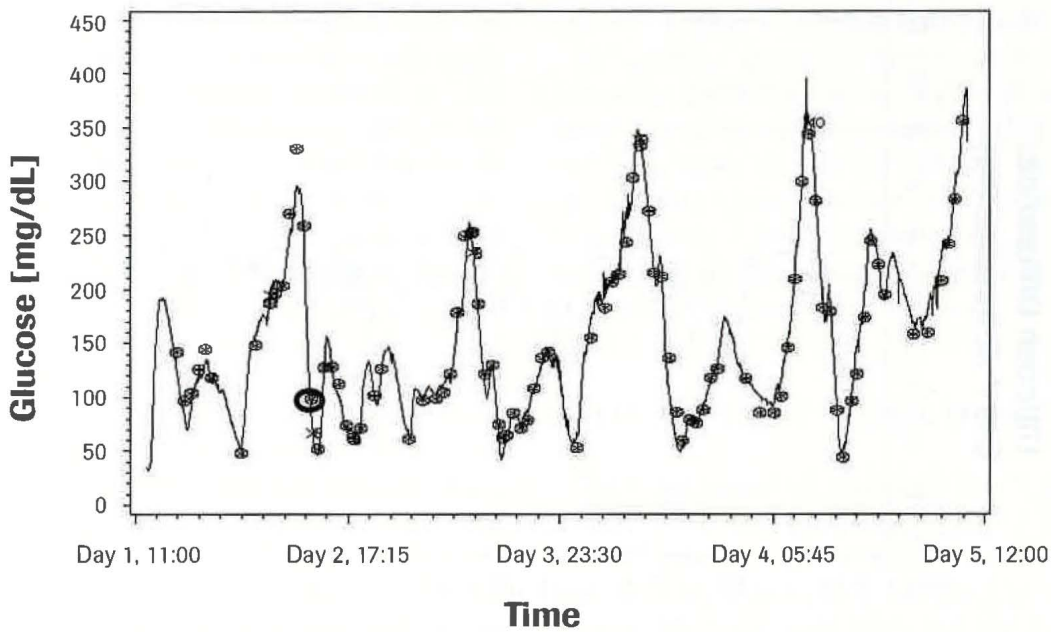

FIG. 4. Selection of calibration point: second chance. The reference value used for calibration is circled.

point calibration on Day 1. The corresponding curve obtained after retrospective calibration over all data points (Fig. 3) (which is the usual approach with retrospective calibration) looks identical and confirms the selection of an "appropriate" calibration point.

Subsequently, another (simulated) prospective calibration point was selected at which the difference between sensor signal and corresponding capillary blood glucose measurement is more pronounced (Fig. 4). Given by the accuracy of the system, such a selection can happen by chance. If the difference at this time point is set to 0, all following differences are shifted by approximately 20% towards the positive region, and a considerable number of points are pushed beyond the upper border of the ±25% range (Fig. 5). The differences range

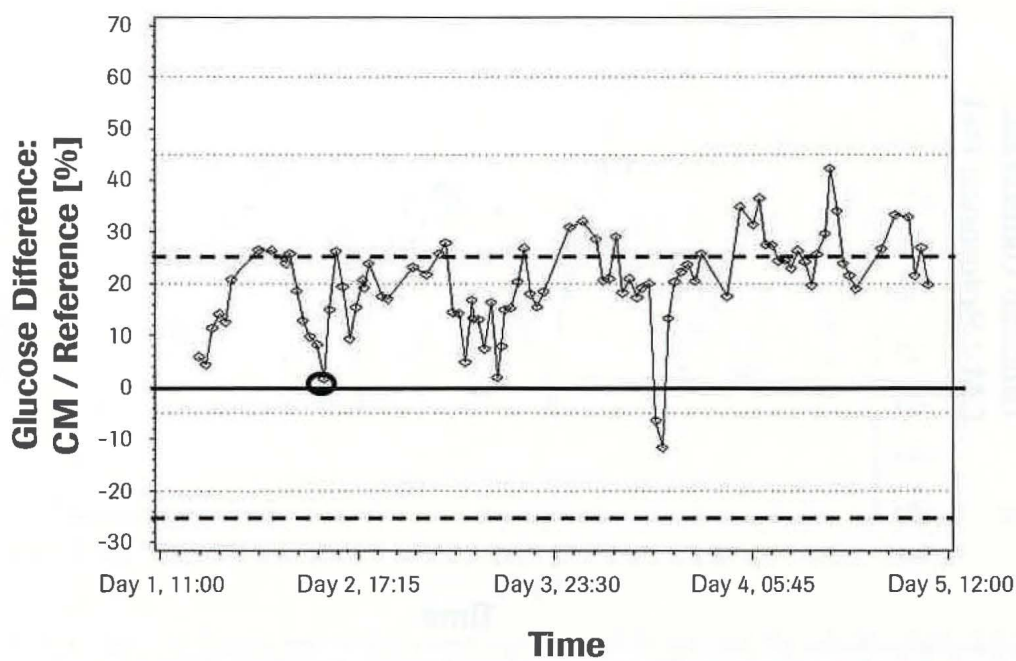

FIG. 5. Selection of calibration point: second chance. Differences are shifted by approximately 20% towards the positive region. The calibration point is circled.

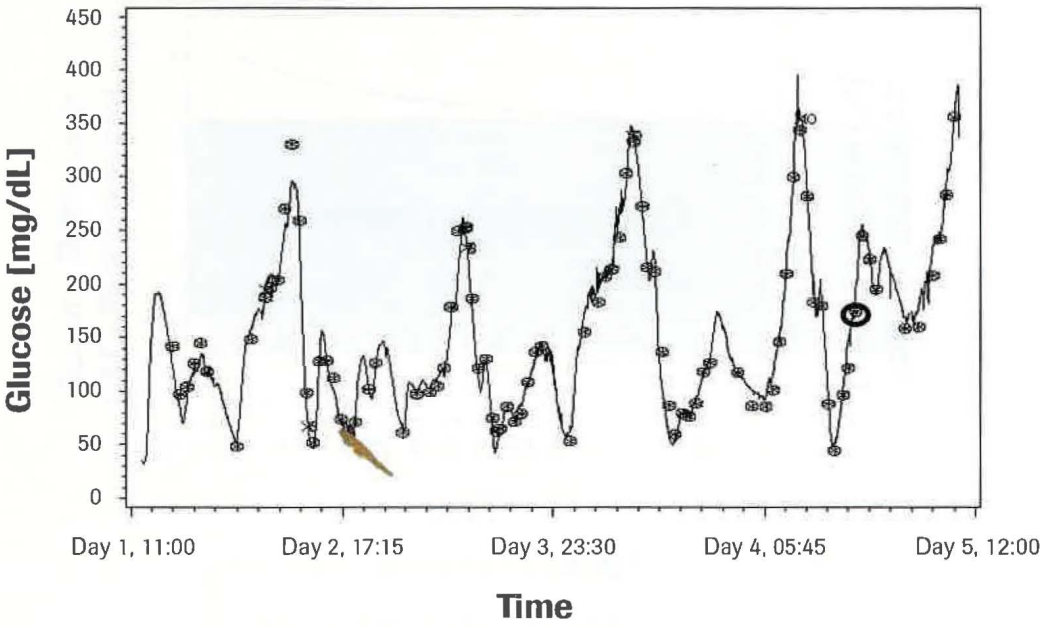

FIG. 6. Selection of calibration point: third chance. The reference value used for calibration is circled.

from −5% to +45%, resulting in a tendency of the CM system to overestimate glucose concentrations (systematic error). With a third calibration point (Fig. 6), the differences are shifted by approximately 20% towards the negative region, and a considerable number of points are pushed beyond the lower border of the ±25% range (Fig. 7). Now the differences range between −45% to +5%, resulting in a tendency of the CM system to underestimate glucose concentrations.

These examples demonstrate how the random "selection" of calibration points from all possible points can introduce a systematic error for all subsequent measurements. Without additional capillary blood glucose measure-

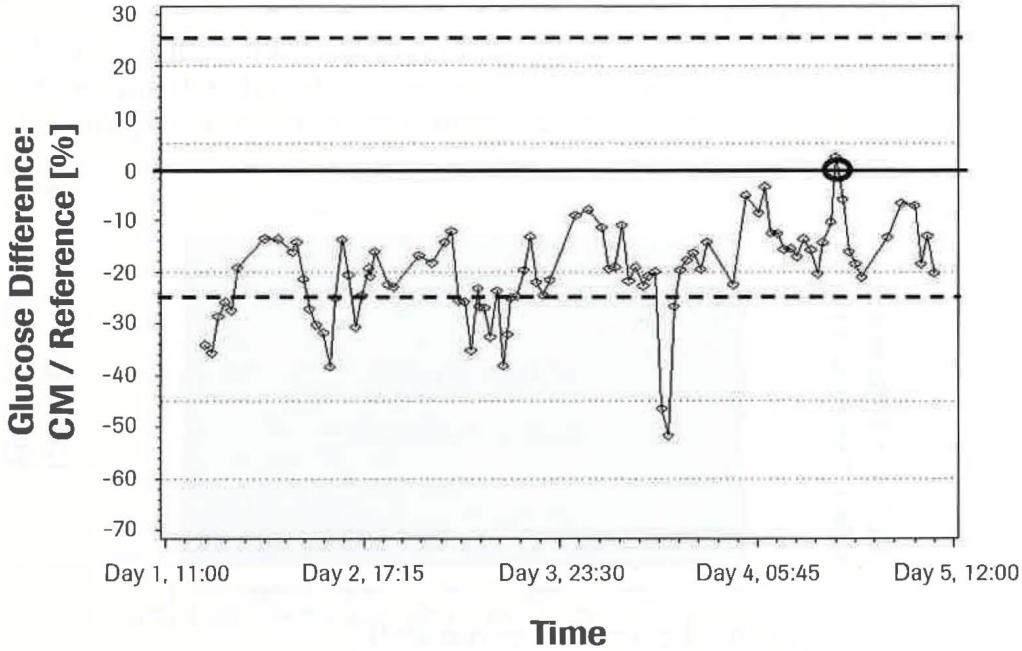

FIG. 7. Selection of calibration point: third chance. Differences are shifted by approximately 20% towards the negative region. The calibration point is circled.

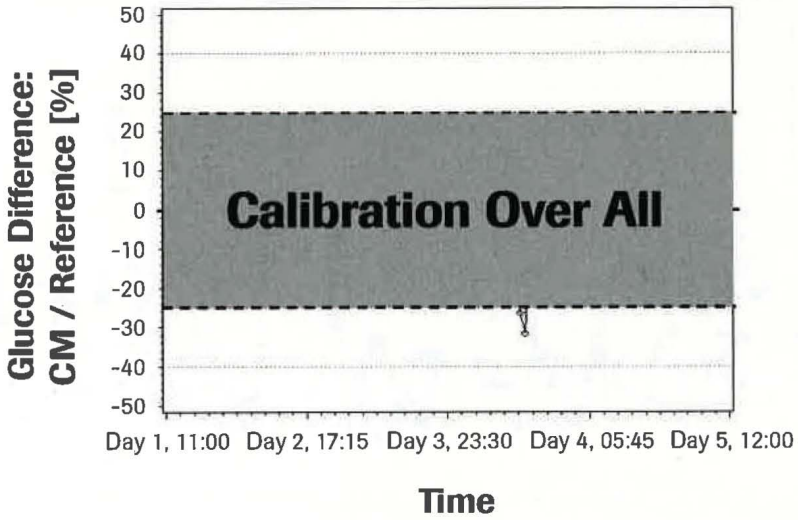

FIG. 8. Error budget for calibration over all data points.

ments after the initial calibration, a patient using such a CM system would be unaware that the glucose values displayed were unreliable.

In a real-life situation the patient has no means of judging whether the displayed capillary blood glucose measurement was taken at the appropriate point in time (i.e., whether it corresponds approximately with the sensor signal or deviates from it to a small or large extent). This fact makes a user-calibration of CM systems in daily life a difficult and critical procedure.

"ERROR BUDGET"

Compared with a retrospective calibration over all data points with an "error budget" in the range between −25% and +25% (Fig. 8), a prospective one-point calibration with arbitrary selection of the calibration points (as described above) has an error budget that is increased by nearly 100% (range between −45% and +45%) (Fig. 9). By use of a prospective multipoint calibration approach the error budget can be reduced, and, after a high number of calibration values, it comes into line with a retrospective calibration overall (Fig. 10), as could be shown before.

ASSESSMENT OF CM SYSTEM QUALITY

There is a need for statistical tools to describe the success of a calibration procedure in quantitative terms, especially for clinical trials com-

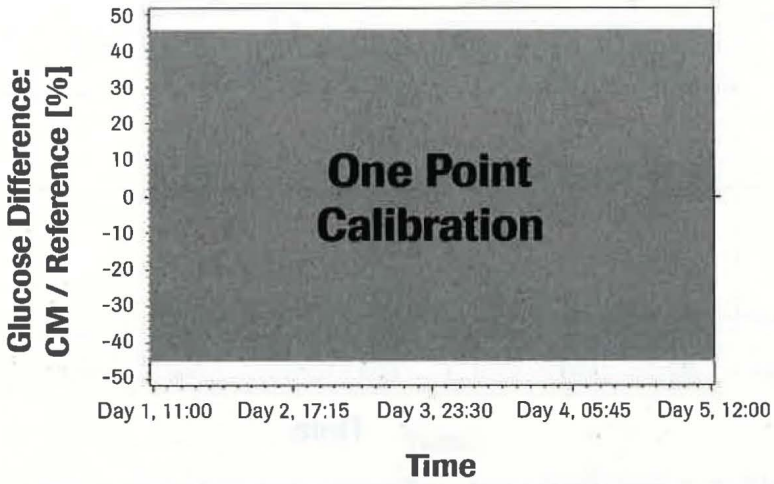

FIG. 9. Error budget for one-point calibration.

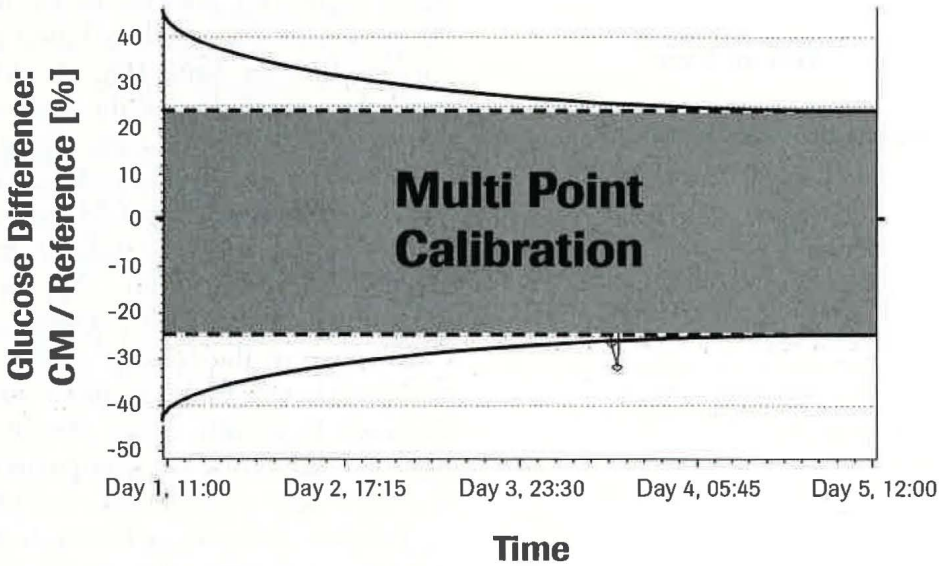

FIG. 10. Error budget for multipoint calibration.

paring longitudinally registered signals of a given glucose sensor to a reference method. Possibly, clinical–experimental studies are needed with continuous reference measurements of blood glucose (e.g., by means of the Biostator). Evaluation of the performance of the same glucose sensors (or different glucose sensors) in the same patient in parallel is helpful for characterization of the properties of the sensor(s).

Since there is no consensus on standard assessment criteria with regard to performance and calibration of CM systems, manufacturers and scientists often have their own preferences. This

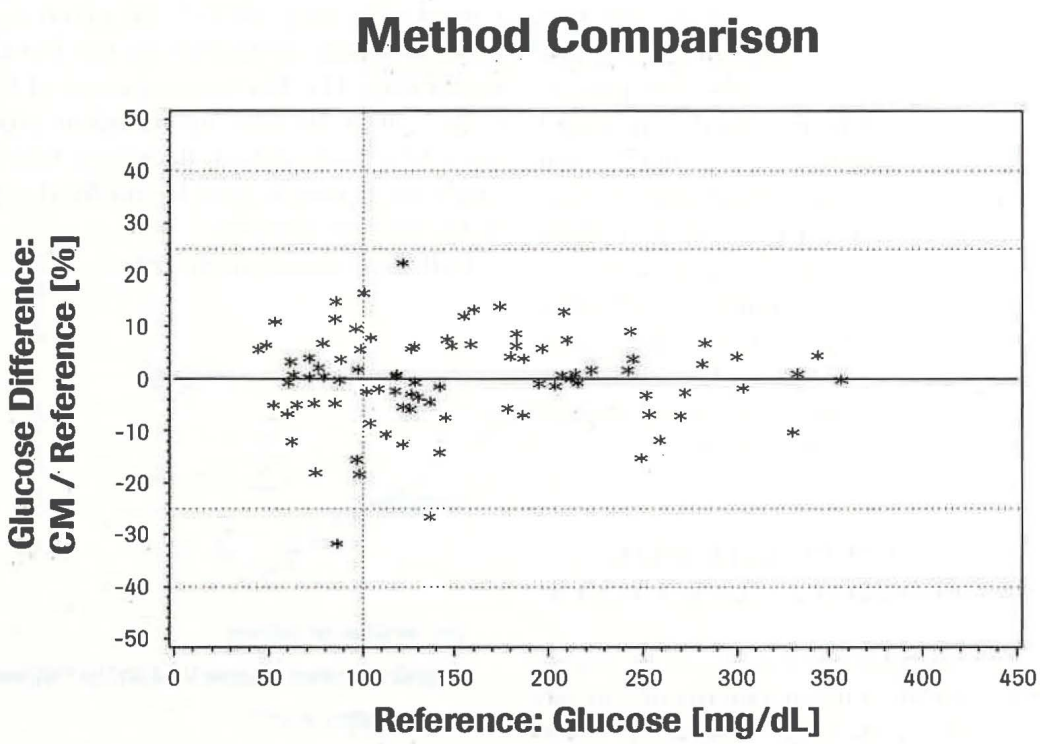

FIG. 11. Comparison of data obtained with a CM system and corresponding reference values by plotting the relative difference (%) between those over the reference values (mg/dL).

System Error

Deviation of single measurements:

$$\Delta_i = \begin{cases} cm_i - bg_i; & if\ bgi \leq 100\ \frac{mg}{dl} \\ \frac{cm_i - bg_i}{bg_i}; & if\ bgi \geq 100\ \frac{mg}{dl} \end{cases}$$

symmetric interval around 0 including 95.5% of the Δ's

- no information on data distribution
- no information on drift

FIG. 12. Calculation of System Error.

impedes comparison of different CM systems and allows focus on those criteria favorable to their "own" system. Ideally, all participants in CM research should use identical assessment criteria in order to establish comparability of the results obtained with different systems.

Commonly, assessment criteria are used retrospectively to evaluate data quality. Since the results of CM measurements are displayed online to the patient, the influence of the calibration process on the quality of the subsequent data must be demonstrated by appropriate criteria.

Most methods and assessment criteria that are currently used for evaluation of CM systems were developed to describe the performance and quality of data obtained with blood glucose meters. Transfer of these criteria from this established area to the novel area of CM does not take into account the fact that these areas differ considerably in the way they describe the clinical reality of patients with diabetes. Therefore, as none of the criteria presented below allows sufficient description of data obtained with CM systems, novel assessment criteria should be developed.

DISPLAY OF CM PROFILE WITH CAPILLARY BLOOD GLUCOSE VALUES

The most straightforward method to assess the data from parallel measurements of a given CM system and capillary blood glucose measurements is to display the course of continuously registered glucose levels together with the results of the capillary blood glucose measurements over time (Fig. 1). In accordance with the established data assessment procedures used for method comparison, paired data sets between the capillary blood glucose values and the corresponding CM values are generated. Thereby, with the data set used as an example here, the original 7,200 data points are reduced to 90 pairs of corresponding values. Calculation of the relative differences (in percentages) between the paired values can be undertaken to eliminate the absolute concentrations and thereby allow comparison of data sets that have been at different absolute levels (Fig. 2). Relative differences fluctuating around the zero line and remaining within the 2SD range, here ±25%, indicate satisfactory performance of the given CM system. This method allows detection of drift of the sensor signal over time.

DATA ANALYSIS WITH ELIMINATION OF TIME INFORMATION

The performance of a CM system can also be assessed without using information about the time course of the glucose profile. Therefore, the relative differences (in percentages) of the paired data (see above) are given against the glucose levels measured by the blood glucose meter (Fig. 11). The consequence of this procedure is that all time information provided by the CM system is lost; however, this is a usual analysis approach used for method comparison with discrete samples.

Different assessment criteria have been de-

% PRESS

$$\%PRESS = \sqrt{\frac{\sum_{i=1}^{n} (cm_i - bg_i)^2}{\sum_{i=1}^{n} bg_i^2}} \times 100$$

- very sensitive on outliers
- depending on mean glucose level and on frequency of swings
- no information on drift

FIG. 13. Calculation of %PRESS.

veloped in order to allow description of the properties of all paired data in a single number. Therefore, from the difference between each pair of CM values (cm_i) and the corresponding capillary blood glucose values (bg_i), assessment criteria as System Error, Predicted Error Sum of Squares (in %) (%PRESS), and Mean Absolute Difference (MAD) are calculated (Figs. 12–14; more detail about the calculations are given there). For the example data set used above this resulted in a System Error of 20%, a %PRESS value of 7.7%, and a MAD value of 5.9%. A disadvantage of these assessment criteria is that identical values can be obtained with CM profiles and capillary blood glucose values that are very different (i.e., a single number does not necessarily provide a reliable estimate of the performance of a CM system).

Using a similar approach, the original CM values (not the relative difference) can also be plotted against corresponding capillary blood glucose values (Fig. 15). A linear regression analysis can provide statistical parameters for the correlation of the paired data.

The error grid analysis was developed to provide clinically meaningful criteria to describe differences between blood glucose values measured with a reference method and a glucose meter in the same samples.[7] The area of the graph is divided into a number of zones with shape and size according to the clinical relevance of pairs of measurements falling into such a sector. Subsequently, the proportion of data points falling into a given sector is determined. Finally, the number of points in the different zones is reported. In line with this approach, es-

MAD

MAD (special def.): median absolute percent difference between CM and reference

$$median\left(\left|\frac{(cm_i - bg_i)^2}{bg_i^2}\right|;\ 1 \le i \le n\right) \times 100$$

- robust on outliers
- no information on data distribution
- no information on drift

FIG. 14. Calculation of MAD.

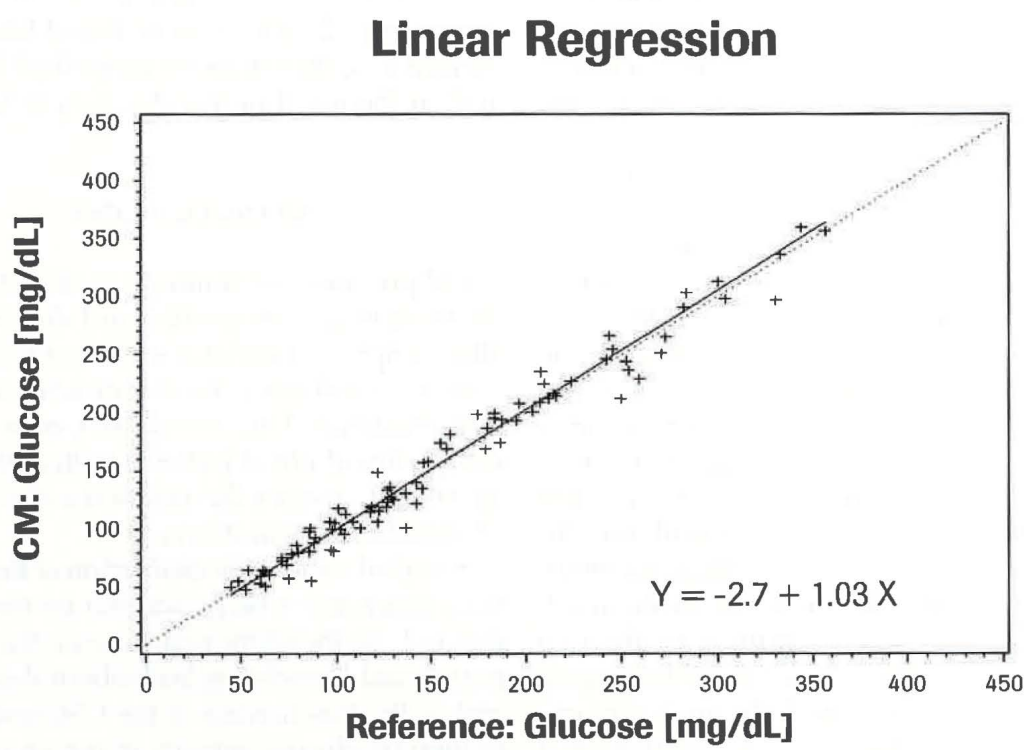

FIG. 15. Linear regression of CM values with corresponding reference values.

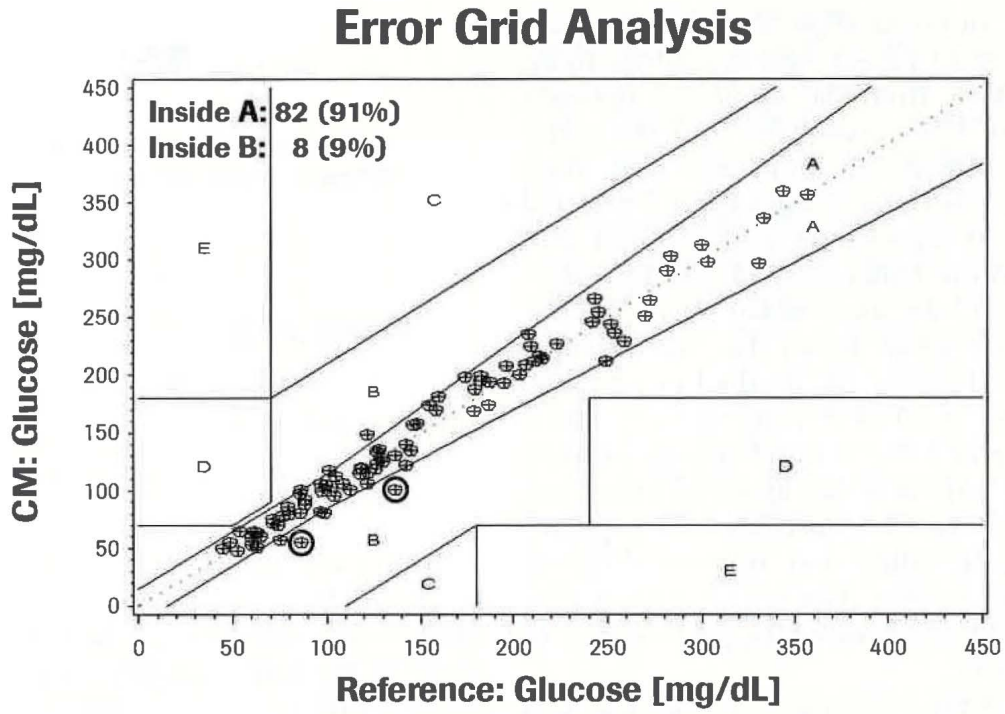

FIG. 16. Error grid analysis. Two data points with clinical relevance are circled.

timation of glucose levels by a given CM system can be plotted against the corresponding values obtained with a reference method, using the reduced data set (see above). This analysis represents an approach to assess not only the accuracy, but also the clinical relevance of the measurement obtained with a given CM system. However, it is clearly limited to those time points at which capillary blood glucose measurements are available, which might not be the case during all relevant times during a day.

With the reduced data set of 90 data points presented above, 82 (91%) lie within Zone A and eight (9%) within Zone B (Fig. 16). Two points of the points in Zone B are special: One represents a measurement where the capillary blood glucose value is within normal range (fasting), while the corresponding CM value is in the hypoglycemic range. The second point is a measurement where the capillary blood glucose value is above the normal range (fasting), while the CM value is within it. In Figure 2, these two points can be identified as the two differences below the −25% border belonging to measurements on Day 3. In such circumstances, reliance on such values displayed by a spot monitoring system by a patient (or his physician) might lead to inappropriate therapeutic decisions. Would this be an issue if a CM system were to be used? The advantage of a CM system is that in practice the "history" of the glucose changes over the preceding hours is available (= trend information). This enables therapeutic decisions to be based both on the current glucose values given by the CM system and on the trend of the glucose profile.

CONCLUSIONS

CM provides substantially more information about daily glucose profiles and should thereby allow improved metabolic control while at the same time reducing the risk of acute metabolic deteriorations. This would not only improve the quality of life of patients with diabetes, but also help to reduce the risk of the development of diabetic complications.

A critical issue is the calibration of the CM system, which must be performed by the patients themselves, therefore requiring on the patients' part sound knowledge both about their disease and of the functioning of the CM system. Calibration of glucose sensors is not an easy task, and a number of different aspects must be taken into account. Some of these aspects have not yet

been satisfactorily investigated, and additional research on the factors influencing calibration of CM systems is required. The conventional assessment criteria used for method comparison were developed for the description of the quality of the performance of blood glucose meters. They are not generally applicable to CM. There is a pressing need for adequate assessment criteria to describe the performance of CM systems that takes full account of all data available (e.g., that takes account of time information). Such novel criteria should then be used preferentially by manufacturers and scientists in order to enable objective evaluation and comparison of CM systems.

ACKNOWLEDGMENTS

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