Comparison of a Needle-Type and a Microdialysis Continuous Glucose Monitor in Type 1 Diabetic Patients

Iris M. Wentholt, MD 1
Marit A. Vollebregt 1
Augustus A. Hart, PhD 2
Joost B. Hoekstra, MD, PhD 1
J. Hans Devries, MD, PhD 1

OBJECTIVE — We examined the reliability of two continuous glucose sensors in type 1 diabetic patients at night and during rapid glucose excursions and verified the hypothesized nocturnal hypoglycemic drift of the needle-type sensor (CGMSgold) and delay of the microdialysis sensor (GlucoDay).

RESEARCH DESIGN AND METHODS — Blood was sampled overnight twice per hour in 13 patients. Rapid-acting insulin was given subcutaneously 30 min after breakfast. Sampling once per minute started 45 min after breakfast and 75 min after insulin injection for 30 min, with the aim of determining peak and nadir glucose values. Mean absolute differences (MADs) between sensor and blood glucose values were calculated. Sensor curves were modeled for all patients using linear regression. Horizontal and vertical shifts of sensor curves from the blood glucose curves were assessed. A vertical shift indicates sensor drift and a horizontal shift sensor delay.

RESULTS — Drift was minimal in the needle-type and microdialysis sensors (−0.02 ± 0.04 mmol/l). Mean ± SD delay was 7.1 ± 5.5 min for the microdialysis sensor (P < 0.001). MAD was 15.0% for the needle-type sensor and 13.6% for the microdialysis sensor (P = 0.013). After correction for the 7-min delay, the microdialysis MAD improved to 11.7% (P < 0.0001).

CONCLUSIONS — The microdialysis sensor was more accurate than the needle-type sensor, with or without correction for a 7-min delay. In contrast to the previous version, the current needle-type sensor did not exhibit nocturnal hypoglycemic drift. Continuous subcutaneous glucose sensors are valuable adjunctive tools for glucose trend analyses. However, considering the large MADs, individual sensor values should be interpreted with caution.

Diabetes Care 28:2871–2876, 2005

C ontinuous glucose sensors have the potential to revolutionize diabetes treatment. Two subcutaneous glucose sensors have been marketed: the needle-type CGMSgold sensor (Medtronic MiniMed, Sylmar, CA) and the microdialysis-based GlucoDay sensor (Menarini Diagnostics, Firenze, Italy). The accuracy of each sensor has been compared with a standard (1–4), but a direct comparison of both sensors is lacking so far. Previous studies have demonstrated a nocturnal drift into the hypoglycemic area for an earlier version of the CGMSgold, the CGMS, but this issue has not been investigated with the CGMSgold (5,6). For the microdialysis monitor, the exact instrument-related time lag has not been established in vivo. This value is especially important when a microdialysis system is being used online as a hypoglycemia alarm. The aim of this study was to examine the reliability of the two sensors in type 1 diabetic patients during the night and during rapid glucose excursions, with special interest in the hypothesized nocturnal hypoglycemic drift of the needle-type sensor and the delay during rapid glucose changes of the microdialysis sensor.

RESEARCH DESIGN AND METHODS — The study was approved by the local ethics committee, and participants gave written informed consent. Thirteen type 1 diabetic patients (9 men) were enrolled. HbA1c was 8.2 ± 0.8% (mean ± SD), BMI was 23.8 ± 3.0 kg/m², age was 34.3 ± 10.7 years, and diabetes duration was 17.2 ± 9.5 years. Exclusion criteria were BMI >30 kg/m², heparin, oral anticoagulant, or corticosteroid use; and skin conditions prohibiting needle insertion.

Continuous subcutaneous glucose sensors
The CGMSgold is a needle-type sensor that quantifies interstitial glucose concentrations via the glucose oxidase reaction with the enzyme immobilized on a subcutaneously inserted electrode. An average glucose concentration is reported every 5 min (7). The sensor requires at least four self-measured blood glucose (SMBG) values per 24 h at ~6-h intervals for retrospective calibration (8). The GlucoDay uses microdialysis to harvest interstitial glucose, perfused at a rate of 10 μl/min. The catheter is connected with a Walkman-sized device containing a glucose biosensor and pump. Glucose is reported every 3 min. For online reading, two calibrations are recommended (9). To minimize variations due to intersensor variability (7), we used the same monitors for each participant.

Study protocol
Both glucose sensors were inserted in the subcutaneous abdominal area, where participants had not administered insulin the week before to prevent possible interference with the measurement. Both glucose sensors were attached strictly according to the manufacturer’s instructions. Sen-
Fluoride tubes. Sampling started at 10:00 A.M. and continued until 8:00 A.M. Because of the extra insulin given at 8:30 A.M., a glucose nadir was expected to occur at 9:00 A.M. If hypoglycemia occurred, the patient received carbohydrates.

At 9:00 P.M., the patient returned to the clinical trial unit. An intravenous catheter was inserted in one arm for blood sampling two times per hour in sodium perfusion buffer and waste product, respectively, until they overlie the blood glucose curve as much as possible and indicate a better fit. The main outcome of this analysis is the measurement SD for each method, derived from the deviations of the measured glucose values from the fitted values. Measurement SD describes how well the fitted curves overlie the actual measurements. Assuming a good fit, which was always aimed for by an optimal choice of the knot intervals, the measurement SD can also be interpreted as a measure of precision or repeatability of the measurement method (sensor or blood glucose). In the second part, the two sensor curves were assumed to have the same shape as the blood glucose curve, again modeled by natural splines at the same knots for blood glucose, but allowing for a possible horizontal and vertical shift away from the blood glucose curve (Fig. E–H). This so-called combined fit resulted in a horizontal and vertical shift for both sensors. Vertical and horizontal shifts are the result of shifting the sensor curves across the vertical and horizontal axes, respectively, until they overlie the blood glucose curve as much as possible and indicate drift and delay, respectively.

The microdialysis sensor was inserted using a dedicated spring system (SenSerter; MiniMed). The patient was instructed to enter the first SMBG after 1 h and to perform an extra calibration if the usual morning insulin injection was postponed, and the patient received a standard breakfast. Frequent sampling (once every minute) started 45 min after breakfast and 75 min after insulin injection and continued for 30 min. In between and thereafter, samples were taken once every 15 min. To avoid unnoticed hypoglycemia, glucose was measured every 5 min using venous blood on a glucose meter (Glucocard Memory 2 system; Menarini), starting from 9:15 A.M. until the end of the experiment. Hypoglycemia was defined as a glucose concentration of ≤3.9 mmol/l (70.0 mg/dl) (10). The intervals were generally 30 min but were 1 h for blood glucose measurements at night. Sometimes the intervals were chosen to be shorter or longer, either because of the sparseness of data or to obtain a better fit. The main outcome of this analysis is the measurement SD for each method, derived from the deviations of the measured glucose values from the fitted values. Measurement SD describes how well the fitted curves overlie the actual measurements. Assuming a good fit, which was always aimed for by an optimal choice of the knot intervals, the measurement SD can also be interpreted as a measure of precision or repeatability of the measurement method (sensor or blood glucose). In the second part, the two sensor curves were assumed to have the same shape as the blood glucose curve, again modeled by natural splines at the same knots for blood glucose, but allowing for a possible horizontal and vertical shift away from the blood glucose curve (Fig. E–H). This so-called combined fit resulted in a horizontal and vertical shift for both sensors. Vertical and horizontal shifts are the result of shifting the sensor curves across the vertical and horizontal axes, respectively, until they overlie the blood glucose curve as much as possible and indicate drift and delay, respectively.

A better fit. The main outcome of this analysis is the measurement SD for each method, derived from the deviations of the measured glucose values from the fitted values. Measurement SD describes how well the fitted curves overlie the actual measurements. Assuming a good fit, which was always aimed for by an optimal choice of the knot intervals, the measurement SD can also be interpreted as a measure of precision or repeatability of the measurement method (sensor or blood glucose). In the second part, the two sensor curves were assumed to have the same shape as the blood glucose curve, again modeled by natural splines at the same knots for blood glucose, but allowing for a possible horizontal and vertical shift away from the blood glucose curve (Fig. E–H). This so-called combined fit resulted in a horizontal and vertical shift for both sensors. Vertical and horizontal shifts are the result of shifting the sensor curves across the vertical and horizontal axes, respectively, until they overlie the blood glucose curve as much as possible and indicate drift and delay, respectively.

**Statistical analysis**

**Curve fitting.** For each patient, morning (7:00 A.M.–10:30 A.M.) and night (10:00 P.M.–7:00 A.M.) periods were analyzed separately. Each analysis consisted of two parts. In the first part, each glucose time curve was fitted separately using least-squares regression and natural splines with knots at equal time intervals, with S-Plus software (Fig. 2A–D) (11).
Bland-Altman analysis. For each sensor, all paired samples were pooled and a mean absolute difference (MAD) [(sensor value - blood glucose)/blood glucose] was calculated. Nighttime blood glucose measurements were coupled to a concomitant or nearest next sensor value. The high blood glucose sampling frequency in the morning allowed us to use a linearly interpolated blood glucose value to be matched to each reported sensor value for MAD calculation. The samples that were matched for calculation of the MAD were also used to determine sensitivity and positive and negative predictive values for hypoglycemic, normoglycemic, and hyperglycemic values for both monitors.

Paired readings were plotted in a Clarke error grid (12). This grid is divided into five zones. Zones A and B represent values that are clinically acceptable: zone A represents values that differ ≤20% from the reference value, and zone B represents values that differ >20% but will not lead to a different treatment decision. Zone C represents values that would result in overcorrecting acceptable glucose values, zone D represents values that are erroneously not corrected, and zone E represents values that would result in opposite treatment, e.g., glucose-lowering therapy in reaction to a hypoglycemic value.

We calculated the number of paired values in each zone of the Clarke error grid using SPSS version 11.5. By using a purpose-built syntax adapted from Clarke et al., problems as previously reported with definition of the “upper A-line” were avoided (13).

In addition to the Clarke error grid analysis (EGA), the recent continuous glucose–error grid analysis (CG-EGA) was applied. This new method allows evaluation of both point and rate accuracy of the sensor readings compared with blood glucose values (14). Sensor readings are regarded as clinically accurate when they fall into the A and B zones of both the point and the rate error grid. Clinically benign errors are those with acceptable point accuracy (A or B zones in the point-EGA) and significant errors in rate accuracy (C, D, or E zones in the rate-EGA), which are unlikely to have clinically negative, therapeutic consequences (14). Finally, the differences between sensor readings and blood glucose measurements were plotted against the average of the blood glucose and sensor measurements in a Bland-Altman plot to evaluate variations in accuracy over the range of measured glucose concentrations (15,16).

RESULTS — In the first patient, the needle-type sensor measurement stagnated in the morning because the evening calibration had erroneously been omitted. Therefore, from this patient we could only analyze the nighttime glucose measurements. Otherwise, there were no recording failures. In the second patient, 38% of the nighttime blood glucose values were lost due to coagulation inside the tube after collection. Six of 13 microdialysis sensor measurements were done with two rather than three calibrations, because stability in blood glucose, required for calibration of this monitor, was not reached at the end of the experiment.
Glucose monitor in type 1 diabetic patients

Curve fitting

Accuracy. Mean measurement SDs were 0.33, 0.25, and 0.30 mmol/l for blood glucose, the needle-type sensor, and the microdialysis sensor, respectively. Morning measurement SDs were 0.29, 0.28, and 0.29 mmol/l, respectively. Nighttime measurement SDs were 0.37, 0.20, and 0.31 mmol/l, respectively. Comparison of the measurement SDs revealed no differences, not between morning and night nor among the three methods (repeated-measures ANOVA, P = 0.14), indicating that separate curve fitting equally accommodated all three measuring methods.

However, there was considerable between-patient and -period variability with measurement SDs ranging from 0.09 to 1.89 mmol/l.

The combined morning and night vertical shift was -0.04 ± 0.87 (mean ± SD) mmol/l (one-sample t test, P = 0.89) for the needle-type sensor and -0.02 ± 0.82 mmol/l (P = 0.95) for the microdialysis sensor, with the minus sign indicating an overall lower value. Morning vertical shift was 0.20 ± 1.37 mmol/l in the needle-type sensor and -0.28 ± 1.05 mmol/l in the microdialysis sensor. Nighttime vertical shift was -0.30 ± 1.08 mmol/l in the needle-type sensor and 0.25 ± 0.97 mmol/l in the microdialysis sensor. For both sensors, there was no evidence that the vertical shift, indicating the drift, differed between morning and night (Wilcoxon’s signed-rank test: needle-type sensor P = 0.28, microdialysis sensor P = 0.23).

Delay. In two instances (needle-type sensor, patients 4 and 7 at night) horizontal shifts of over 1 h were found. This is probably an artifact from the analysis method caused by either a considerable difference in curve shapes or nearly straight curves. The latter makes it difficult to identify a horizontal shift and thus the delay. Therefore, the nighttime horizontal shift values for the needle-type sensor in patients 4 and 7 were omitted, whereas morning needle-type sensor values were not obtained in patient 1 as explained above. Thus, morning accuracy and delay for the needle-type sensor were analyzed in 10 patients and for the microdialysis sensor in 13 patients. The mean ± SD horizontal shift over night and morning was 7.1 ± 5.5 min for the microdialysis sensor (one-sample t test, P < 0.001). As already indicated by the SD, there was considerable between-patient and -period variability, with a range of -9.2 to 20.5 min. A minus sign indicates a shift to the left with respect to the blood glucose curve. For the needle-type sensor, there was no evidence of a systematic horizontal shift (mean −2.2 ± 6.2 min, P = 0.28), with a range of −20.3 to +15.8 min. For both sensors, the horizontal shift, indicating delay, did not appear to differ significantly between morning and night (Wilcoxon’s signed-rank test: needle-type sensor P = 0.12, microdialysis sensor P = 0.46).

MAD, hypoglycemia detection, Clarke EGA, CG-EGA, and Bland-Altman analyses

MAD was 15.0 ± 12.2% (735 paired samples) for the needle-type sensor and 13.6 ± 10.2% (1,156 paired samples) for the microdialysis sensor (independent samples t test: P = 0.013). After correction for the 7-min delay, microdialysis sensor MAD improved from 13.6 to 11.7 ± 9.8% (independent samples t test: P < 0.0001 vs. both previous microdialysis and needle-type sensor MADs).

A separate MAD calculation per glucose range for the needle-type, microdialysis, and corrected microdialysis sensors resulted in an MAD in the hypoglycemic range (≤3.9 mmol/l) of 24.1% (59 paired samples, blood glucose 3.2 ± 0.4 mmol/l), 17.3% (80 paired samples, blood glucose 3.2 ± 0.4 mmol/l), and 14.5% (82 paired samples), respectively; an MAD in the normoglycemic range (3.9 < blood glucose < 10.0 mmol/l) of 15.7% (359 paired samples, blood glucose 6.6 ± 1.7 mmol/l), 15.5% (549 paired samples, blood glucose 6.7 ± 1.7 mmol/l), and 12.9% (536 paired samples); and an MAD in the hyperglycemic range (≥10.0 mmol/l) of 12.5% (317 paired samples, blood glucose 13.9 ± 2.8 mmol/l), 11.1% (527 paired samples, blood glucose 14.0 ± 2.8 mmol/l), and 9.9% (525 paired samples). During normoglycemia, the microdialysis and needle-type sensors revealed nearly similar MADs (independent samples t test: P = 0.839). However, during hypo- and hyperglycemia, the microdialysis sensor was more accurate than the needle-type sensor (independent-samples t test: P = 0.023 and P = 0.040, respectively). The MAD for the 7-min–corrected microdialysis-based sensor was significantly lower than the needle-type sensor MAD in all three ranges, with P values ranging from 0.001 during hypo- and normoglycemia to <0.0001 during hyperglycemia (independent-samples t test).

Positive predictive values for hypoglycemic values were 56.9% for the needle-type sensor and 68.2% for the microdialysis sensor. Negative predictive values were 96.2% for the needle-type sensor and 98.1% for the microdialysis sensor. Sensitivity and specificity for detecting hypoglycemic blood glucose values were 55.9 and 96.3%, respectively, for the needle-type sensor and 75.0 and 97.4%, respectively, for the microdialysis sensor. Sensitivity for detecting normoglycemic blood glucose values was the same for both sensors (84.8%). During hyperglycemia, sensitivity was 84.7 and 90.1% for the needle-type and microdialysis sensors, respectively. Clarke EGA for needle-type and microdialysis sensors indicated that 72.4% (range 25.0–96.6%) and 76.0% (52.8–98.0%) of the paired values were in zone A, 24.4% (0–58.1%) and 22.3% (2.0–47.2%) were in zone B, 0 and 0.1% (0–1.0%) were in zone C, and 4.1% (0–32.1%) and 1.5% (0–10.6%) were in zone D. No readings fell in zone E.

According to the CG-EGA analysis, both sensors showed no difference in accuracy. The percentages of the needle-type and microdialysis sensor readings that were clinically accurate or resulted in benign errors were 60.0% (60.0% accurate and 0% benign) and 57.2% (57.2% accurate and 0% benign), respectively, at hypoglycemia, 100% (93.8% accurate and 4.2% benign) and 100% (98.1% accurate and 1.9% benign), respectively, at normoglycemia, and 97.6% (95.2% accurate and 4.2% benign) and 97.8% (93.4% accurate and 4.4% benign), respectively, at hyperglycemia.

The Bland-Altman plot (Fig. 3) showed that sensor and blood glucose measurements differed considerably and that during hypoglycemia especially, needle-type sensor readings exhibited a more pronounced decline in accuracy than microdialysis sensor readings. This finding corresponds with the substantial difference between the separately calculated MADs in the hypoglycemic range (24.1% for CGMSgold vs. 17.3% for GlucoDay).

CONCLUSIONS — We used both classic methods (MAD, Clarke error grid, hypoglycemia detection accuracy, and Bland-Altman analyses) and novel methods (least-squares linear regression analysis including separate and combined curve fitting and CG-EGA) to analyze sensor accuracy, both during periods of stable glycemia and during rapid but physiological glucose excursions.
According to the classic methods, the accuracy of both sensor systems was in line with previously reported values (1, 2). The rapid glucose excursions in the morning apparently did not result in deteriorated accuracy for either sensor, because no significant differences were detected between the morning and nighttime vertical shift and MAD. The microdialysis sensor, especially when corrected for the 7-min delay, exceeds the needle-type sensor in accuracy (13.6% [corrected 11.7%] vs. 15.0%). Correction for the 7-min delay resulted in a 2% lower MAD for the microdialysis sensor in each glucose range. Bland-Altman analyses and separately calculated MADs per glucose range demonstrated that the accuracy of the needle-type sensor deteriorates during hypoglycemia, with an MAD of 24.1% in that range. To a lesser extent, the same result was seen with the microdialysis sensor (MAD 17.3%). The reason that the CG-EGA did not show a difference in performance in the hypoglycemic area, contrary to the other assessment tools, needs further investigation.

Figure 3—Bland-Altman plots for the needle-type sensor CGMSgold (A) and the microdialysis sensor GlucoDay (B). The x-axis represents the average of blood and sensor glucose measurements, and the y-axis represents the difference between sensor and concomitant blood glucose measurements expressed as percentage of value on the x-axis. The difference between blood glucose and sensor readings is 0% at the horizontal solid line. The long dashed line is drawn at the mean difference (−1.4% for the needle-type and −1.6% for the microdialysis sensor); dotted lines are drawn at the mean difference ± 1.96 times the SD of the differences.
Glucose monitor in type 1 diabetic patients

As indicated by the vertical shift derived from combined curve fitting, the currently available needle-type sensor does not exhibit a nocturnal hypoglycemic drift, in contrast to the previous version. Both sensors perform similarly during the day and night, without significant differences in accuracy. The hypothesized delay for the microdialysis system has been quantified (7 min) by the horizontal shift. This delay can be corrected for retrospectively but has implications for prospective use of microdialysis systems as an alarm for hypo- or hyperglycemia.

The advantage of least-squares linear regression analysis with either separate or combined curve fitting is that all measurements are used for analysis without any data exclusion as when paired samples only, such as MAD or EGA, are used. Furthermore, combined curve fitting offers an advantage over MAD and EGA by its ability to assess systematic over- or underestimation and a delay. The vertical shift suggests an almost negligible difference between needle-type and microdialysis sensors (−0.04 vs. −0.02 mmol/L), whereas accuracy based on MAD was better in the microdialysis than in the needle-type sensor. This illustrates that both methods are complementary. The least-squares regression method is sensitive to systematic under- or overestimation, whereas it flattens out overestimated and underestimated glucose values.

Our method to obtain a rapid rise and fall in glucose level, induced by food intake and delayed subcutaneous insulin injection in an increased dose, is a modification of a test in which insulin was injected intravenously (17). Because intravenous insulin may induce a non-physiologically rapid decline in glucose level, we feel our method resembles real life circumstances more closely.

Despite having used the same sensors and insertion sites for all patients, both sensors showed considerable interpatient variability. For example, the underestimated glucose values reported by the needle-type sensor, falling in zone D of the Clark error grid (4.1%) and corresponding points below the horizontal line in the hyperglycemic part (12.0 mmol/L) of the Bland–Altman plot (Fig. 3A), all originated from one patient. The causes of this interpatient variability need further investigation. The number of patients, i.e., 13, was limited, and the research setting was not in accordance with the daily life situation. Thus, it may not be possible to obtain data of the same quality in clinical practice.

In summary, the microdialysis-based sensor exceeds the needle-type sensor in accuracy, with and without correction for a 7-min delay. The accuracy of the needle-type sensor is especially worst during hypoglycemia. The recent version of the needle-type sensor seems to have been improved with respect to the nocturnal hypoglycemic drift, which was not detected in the present study. The current continuous subcutaneous glucose sensors appear to be valuable adjunctive tools for glucose trend analyses. However, taking into account their considerable MADs, one should interpret individual sensor values with caution.

Acknowledgments—The study was financially supported by Menarini Diagnostics Benelux, Valkenburg, the Netherlands. Sensors were obtained free of charge from Medtronic MiniMed, Heerlen, the Netherlands. We acknowledge Rutger van Haaften for his valuable contribution.

References