Detection of Hypoglycemia With the GlucoWatch Biographer

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OBJECTIVE — Hypoglycemia is a common acute complication of diabetes therapy. The GlucoWatch biographer provides frequent and automatic glucose measurements with an adjustable low-glucose alarm. We have analyzed the performance of the biographer low-glucose alarm relative to hypoglycemia as defined by blood glucose ≤3.9 mmol/l.

RESEARCH DESIGN AND METHODS — The analysis was based on 1,091 biographer uses from four clinical trials, which generated 14,487 paired (biographer and blood glucose) readings.

RESULTS — The results show that as the low-glucose alert level of the biographer is increased, the number of true positive alerts (alarm sounds and blood glucose ≤3.9 mmol/l) and false positive alerts (alarm sounds but blood glucose >3.9 mmol/l) increased. When analyzed as a function of varying low-glucose alert levels, the results show receiver operator characteristic curves consistent with a highly useful diagnostic tool. Setting the alert level from 1.1 to 1.7 mmol/l above the level of concern is likely to optimize the trade-off between true positives and false positives for each user. When the same blood glucose data are analyzed for typical monitoring practices (two or four measurements per day), the results show that fewer hypoglycemic events are detected than those detected with the biographer.

CONCLUSIONS — The frequent and automatic nature of the biographer readings allows more effective detection of hypoglycemia than that achieved with current medical practice.

H ypoglycemia is a common acute complication of diabetes therapy. The frequency of severe hypoglycemia has been shown to increase with more intensive treatment. Increasing the frequency of glucose measurements, regardless of the technique used, makes it possible to detect a greater number of hypoglycemic events. However, as many as seven glucose measurements per day may fail to detect hypoglycemic events (1).

A device providing automatic readings could make frequent monitoring easier and enable an alarm to be sounded in response to glucose readings below user-selected alert levels. Such an alarm could reduce the risk of hypoglycemia, making intensive therapy safer and more acceptable for patients.

The GlucoWatch biographer (Cygnus, Redwood City, CA) provides frequent, automatic, and noninvasive glucose measurements—up to three readings per hour for as long as 12 h after a blood glucose

measurement for calibration. Clinical studies in controlled and home environments have demonstrated high accuracy and precision (2,3). The results presented here evaluate the hypoglycemia alert performance in a large and demographically diverse patient population using the biographer both in controlled and normal daily environments. The accuracy and precision results from these studies have been described (4).

The performance of the hypoglycemia alert depends on the selection of a low-glucose alert level that will trigger an audible alarm. The performance of the alert function can be best evaluated by an analysis of the receiver operator characteristic (ROC) curves (5). The ROC curve is a plot of the sensitivity (true positive fraction [TPF]) versus 1.0 − specificity (false positive fraction [FPF]) for a series of possible low-glucose alert levels.

RESEARCH DESIGN AND METHODS

Noninvasive glucose extraction and detection

The biographer extracts glucose through the skin by reverse iontophoresis and measures the extracted sample using an electrochemical biosensor. Iontophoresis is a technique whereby a low-level electric current (0.3 mA/cm^2 in these studies) is passed through the skin between an anode and a cathode (6). The current is carried primarily by the migration of sodium ions toward the cathode. Uncharged molecules (e.g., glucose) are carried along by convective transport (electroosmosis) (7,8). The amount of glucose extracted at the cathode has been demonstrated to correlate with blood glucose in diabetic subjects (9). In the biographer, the extracted glucose is measured by an amperometric biosensor using detection of H_2O_2 generated by the glucose/glucose oxidase reaction. The operating principles of the biosensor are described elsewhere (10–12).

The biographer provides readings every 20 min after calibration using a fingerstick blood glucose measurement taken after a 3-h equilibration period. This sin-

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Table 1—*Description of the protocols used*

Study name	Accuracy	Home simulated	Home environment	Lab method comparison
Environment	Controlled clinic	Home simulated	Home	Home simulated
Duration (days)	1	2	5 (Wed. through Sun.)	1
Biographers worn per day	2	1	1	2
Calibrating BG device	HemoCue Photometer	One Touch Profile	One Touch Profile	YSI Analyzer
Comparative BG device	HemoCue Photometer	HemoCue Photometer	One Touch Profile	YSI Analyzer
Frequency of comparative BG measurements (*n*/h)	2	2	1	1
Number of biographer uses	406	212	420	53
Total number of paired points*	7,181	3,829	3,060	417

Data are *n*, unless otherwise indicated. *Includes pairs where the biographer reading and/or the blood glucose value are outside the range of 40–400 mg/dl. BG, blood glucose.

gle-point calibration, which accounts for variability in both biosensor sensitivity and skin permeability, is used to convert subsequent biosensor measurements into glucose readings. A signal-processing algorithm (12) is programmed into the biographer software. The reading lags behind the corresponding blood glucose value by ~17 min.

Data integrity screens in the biographer software detect spurious data points resulting from such sources as electrical noise, high background currents, and open or short circuits. The presence of data points not conforming to objective a priori criteria results in the disregarding (or skipping) of a glucose reading. The biographer also contains skin temperature and skin conductance sensors. The latter is directly related to the amount of sweat on the surface of the skin. Because large temperature changes or the presence of glucose in sweat can confound the glucose measurement, once the output from either of these sensors exceeds a predetermined threshold, the measurement for that cycle will be skipped. These data-screening methods thus prevent potentially inaccurate glucose readings. In the studies presented here, ~20% of all readings were skipped because of data integrity screens.

Study designs

Four clinical studies were performed, each with institutional review board approval. Accuracy was evaluated in a controlled clinic setting, a simulated home environment, and the home environment. An additional laboratory method comparison study evaluated accuracy versus a laboratory standard method (YSI analyzer; Yellow Springs Instruments).

Biographer readings were compared to serial capillary blood glucose measurements performed with a variety of instruments. Subjects wore the biographer for 15-h sessions (3-h equilibration and 12-h measurement periods). In the clinic setting, glucose levels were manipulated to produce periods of hypoglycemia and hyperglycemia. All subjects were adults (18 years of age and older) with type 1 or type 2 diabetes requiring insulin treatment. The biographer readings were masked from the patients and investigators during the study period. All dose adjustments for insulin were completed using blood glucose measurements. Table 1 summarizes the design of the clinical studies along with the number of biographer uses and paired points. Patient diaries were used to record the times of meals and insulin injections. The diaries did not require the subjects to record symptoms of possible hypoglycemia.

Data analysis methods

Data download and analyses of accuracy and precision are described elsewhere (2–4). The objective of this analysis was to evaluate the ability of the biographer to correctly detect hypoglycemia as determined by the comparative blood glucose value. This analysis was completed by defining hypoglycemia as blood glucose ≤3.9 mmol/l and varying the biographer low-glucose alert level. At each alert level, each biographer reading was evaluated as either a true positive (TP), false positive (FP), true negative (TN), or a false negative (FN). The definitions of each of the terms are as follows:

- Hypoglycemic event: blood glucose ≤3.9 mmol/l

- Biographer low-glucose alert level: threshold below which the biographer would trigger the audible alarm
- TP: blood glucose ≤3.9 mmol/l and biographer less than or equal to the low alert level
- FP: blood glucose >3.9 mmol/l but biographer less than or equal to the low alert level
- TN: blood glucose >3.9 mmol/l and biographer more than the low alert level
- FN: blood glucose ≤3.9 mmol/l but biographer more than the low alert level

Sensitivity and specificity were defined by the following equations and determined at seven low-glucose alert levels (3.9, 4.4, 5.0, 5.6, 6.1, 6.7, and 7.2 mmol/l).

$$\text{sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{specificity} = \text{TN}/(\text{TN} + \text{FP})$$

These results were then used to prepare the ROC curves.

The TPF is the same as the sensitivity and reflects the frequency with which the biographer correctly identified hypoglycemia of all occasions in which the blood glucose test result was ≤3.9 mmol/l. The FPF is calculated by subtracting the specificity from 1.0. The FPF reflects the frequency with which the biographer incorrectly identified hypoglycemia of all occasions in which the blood glucose test result was >3.9 mmol/l.

Two types of hypoglycemic events were analyzed. First, only paired biographer readings and blood glucose values were analyzed. For this paired-point analysis, the comparative blood glucose result
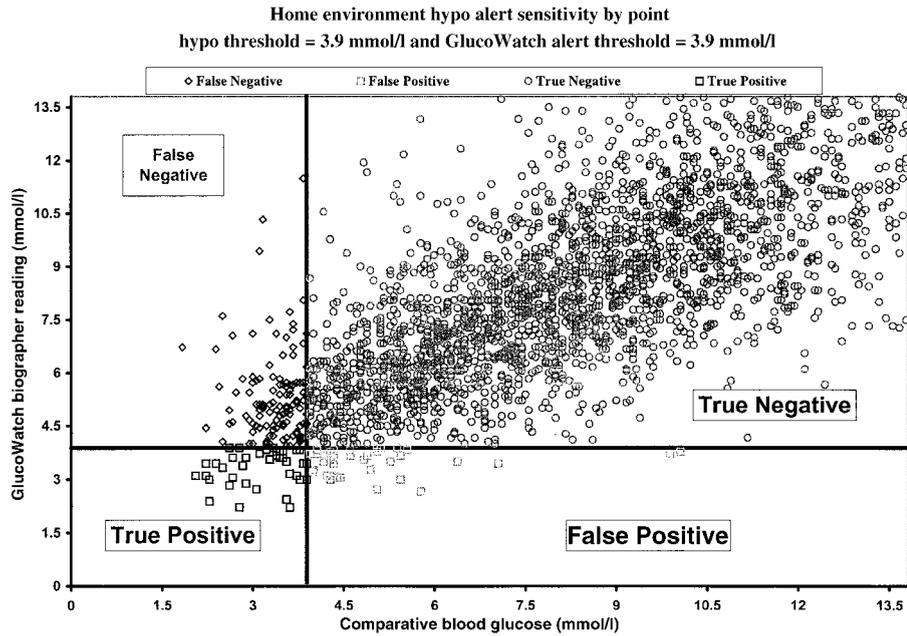
Home environment hypo alert sensitivity by point
hypo threshold = 3.9 mmol/l and GlucoWatch alert threshold = 3.9 mmol/l

Figure 1—*A correlation plot of the GlucoWatch biographer versus blood glucose values for the home-environment study.*

must have been obtained in the time period between 10 and 20 min before the biographer reading. The results of all studies were analyzed in this manner. In addition, the home-environment data were analyzed for all blood glucose ≤3.9 mmol/l, even if there were no paired biographer readings. This was completed by evaluating biographer readings immediately surrounding the hypoglycemic event.

RESULTS — In the home-environment study, there were 247 hypoglycemic events of 5,305 blood glucose measurements. Of those 247 hypoglycemic events, 160 had paired biographer readings of 3,060 paired values.

A plot of the biographer readings versus comparative blood glucose values is shown in Fig. 1. Superimposed on Fig. 1 are lines showing the definition of hypoglycemia (blood glucose ≤3.9 mmol/l) and one choice for the biographer low-glucose alert level (3.9 mmol/l). These lines divide the plot into quadrants of TP, FP, TN, and FN values. Tabulation yields values for TP, FP, TN, and FN of 39, 36, 2,864, and 121, respectively. From these data, values for sensitivity and specificity are 0.24 and 0.99, respectively. Hence, when the low-glucose alert was set at 3.9 mmol/l, the biographer correctly identified 24% (39/[39 + 121]) of the hypogly-

cemic events. In addition, 99% (2,864/ [2,864 + 36]) of the time the biographer correctly identified a value >3.9 mmol/l in the absence of hypoglycemia.

The sensitivity and specificity were obtained at low-glucose alert levels of 4.4, 5.0, 5.6, 6.1, 6.7, and 7.2 mmol/l by a similar graphical tabulation. Figure 2 shows the ROC curve constructed from

these data by plotting sensitivity (or TPF) vs. 1.0-specificity (or FPF). A table of the data is shown in Fig. 2. Results show that increasing the alert level increased the sensitivity and 1.0-specificity. The TPF increased from 24 to 95%, and the FPF increased from 1 to 29%, as the alert level increased from 3.9 to 7.2 mmol/l.

A similar analysis was performed for all clinical trials and showed similar results (data not shown). In each case, increasing the low-glucose alert level from 3.9 to 7.2 mmol/l resulted in an increase in TPF to >90% and an increase in FPF to ~30%. Finally, similar results were also obtained when hypoglycemia was defined as blood glucose either <3.3 or 2.8 mmol/l, albeit with fewer events (data not shown).

The analysis of paired data requires that biographer readings exist for each comparative blood glucose measurement. Biographer readings may be unavailable for a number of reasons. For example, the home-environment data shows that of the 247 hypoglycemic events, 160 paired biographer readings were available. Of the remaining 87 hypoglycemic events, 24 biographer readings were unavailable because the event occurred before or during calibration or after the biographer had shut off. The final 63 biographer readings were unavailable because the blood glucose measurement was obtained at a time that differed from the biographer reading

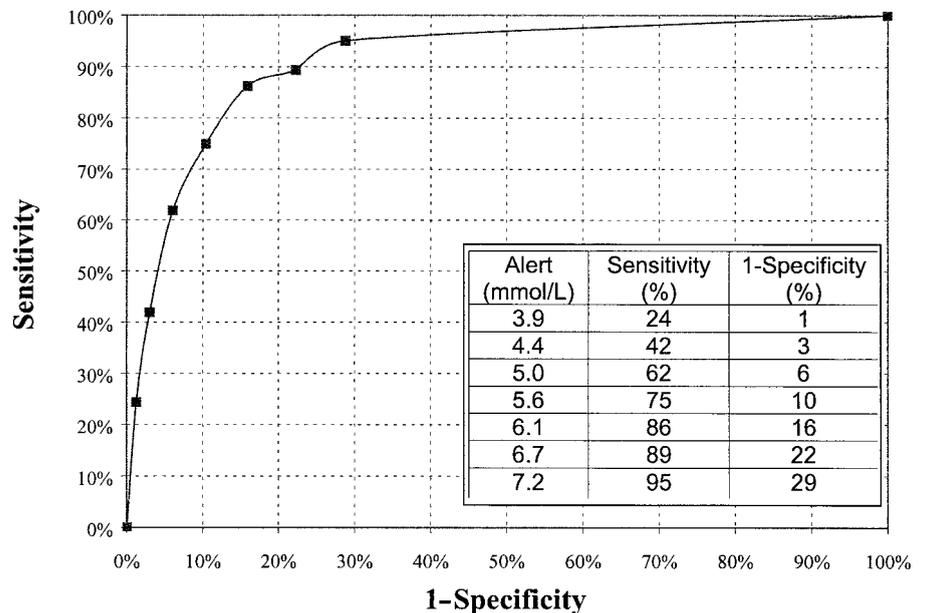| Alert (mmol/L)	Sensitivity (%)	1-Specificity (%)
3.9	24	1
4.4	42	3
5.0	62	6
5.6	75	10
6.1	86	16
6.7	89	22
7.2	95	29

Figure 2—*ROC curve for the data from the home-environment study.*

by >15 ± 5 min or the blood glucose reading coincided with a skipped biographer reading. However, because of the frequent and automatic nature of the data, the nearest biographer readings can be used for analysis. In addition, because perspiration can be associated with hypoglycemia, the biographer is designed to sound an alarm when a reading is skipped because of perspiration. Using the surrounding biographer readings with a low-glucose alert level of 5.6 mmol/l and the perspiration alarm, the sensitivity is 75%, or 47 of 63. This value is identical to that seen in the paired-point analysis.

CONCLUSIONS — The results show that as the biographer low-glucose alert level is increased, TPF increases; however, FPF also increases. In the home-environment study, increasing the alert level from 3.9 to 5.6 mmol/l increases the TPF by ~50%, with a <10% increase in FPF. However, a further increase of the alert level to 7.2 mmol/l yielded a relatively small increase in TPF (<20%), whereas the FPF increased by 16%. Note that the TPF values are an underestimate because the comparative blood glucose meter is assumed error-free and all error is associated with the biographer.

The trade-off between TPF and FPF is best shown in the ROC curves. The optimal alert level is where the slope of the ROC curve is equal to the unity (5). The results of the home-environment study suggest that the optimal alert level (for detection of blood glucose ≤3.9 mmol/l) is ~5.6 mmol/l. Under these conditions, the user obtains the optimal TPF values (75%) relative to the FPF values (10%).

The ROC curves were analyzed for all four studies (data not shown). In each case, a biographer low-glucose alert level near 5.6 mmol/l yields optimal results, with TPF ranging from 75 to 89% and FPF from 10 to 17%. The results are remarkably similar among the studies regardless of differences in the calibrating and comparative meters as well as the study environment; this suggests that the hypoglycemia alert function is robust.

Setting the biographer alert level at 5.6 mmol/l results in an "indifference zone," where the alarm is activated, but the blood glucose value is between 3.9 and 5.6 mmol/l. Although these blood glucose levels are not in the hypoglycemic range, the alert may provide an early warning of a trend downward into that range. Therefore, sounding the alarm is both useful and appropriate. Note that a large number of the FP points are in this indifference zone.

The analysis of TPF and FPF requires both a biographer reading and a blood glucose value within the specified timing window. Because blood glucose was measured only once or twice per hour (depending on the study), it is possible that some hypoglycemic events were excluded from the analysis because no blood glucose test was done at an opportune time. Of greater concern are situations with a known hypoglycemic event (blood glucose ≤3.9 mmol/l) that were excluded from the analysis because of the absence of a biographer reading. For a number of hypoglycemic events, no paired biographer reading was available because of skipped readings or blood glucose data that differed in time from the biographer reading by >15 ± 5 min. Because of the frequent and automatic nature of the biographer data, however, the immediately adjacent readings can be used to detect hypoglycemia. An analysis of those adjacent biographer readings, which also includes the perspiration alarm, yields sensitivity values that are similar to those obtained with paired values. Thus, although the biographer will skip readings that may be aberrant, the alert function remains because of the frequent and automatic nature of the device.

Skipped readings caused by perspiration are of particular interest because perspiration can be a symptom of hypoglycemia. Research subjects report that perspiration skips occur on occasions when there is no doubt that they are sweating. In the home-environment study, there were a total of 13,573 biographer readings from 420 biographer applications. A total of 422 readings (3.1%) were skipped because of perspiration. Of the 247 hypoglycemic events in this study, 11 (4.5%) were associated with biographer skips caused by perspiration. Thus, although perspiration sufficient to cause skipped readings may be more prevalent during hypoglycemia, the overall frequency of readings skipped because of perspiration during hypoglycemia in home use is quite low.

The trade-off between TPF and FPF is a fundamental limitation of any diagnostic test used to screen for a disease or condition of concern. Another limitation specific to the biographer is the lag time between blood glucose levels and biographer readings. With the biographer, the primary component of the lag time is the 20-min measurement cycle that results in a time-averaged glucose reading. An additional source of lag time is the mass transfer between blood and peripheral tissue that has been observed in studies with implanted subcutaneous sensors and microdialysis devices (1). Clearly differentiating between these two sources of lag time will require further studies using controlled environments and standardized variations in blood glucose levels that include insulin-induced hypoglycemia.

In practice, lag time is an additional reason why it is important to select a conservative setting for the low-glucose alert level. In actual use, the patient and/or health professional can change the low-glucose alert level to suit the occasion. For example, if it is crucial that the subject be aware of hypoglycemic events (such as when driving or operating machinery), the alert level could be set higher. Of course, this will also result in increased FP readings. However, by checking the readings immediately preceding the activity and checking for any symptoms, the patient can quickly decide whether further action is needed. Conversely, if it is important to have high certainty of hypoglycemia when the alarm sounds, the alert level can be set lower. In this way, fewer false alerts will occur.

The utility of this new device must be assessed relative to the available alternatives. Currently, patients with diabetes must rely on symptoms of possible hypoglycemia and the limited number of blood glucose tests performed each day. Thus, it is useful to evaluate the detection of hypoglycemia from the same data set using typical blood glucose monitoring practices. Using mealtimes from the patient diaries, the blood glucose data from the home-environment study were analyzed for two commonly recommended testing frequencies.

First the detection of hypoglycemia (blood glucose ≤3.9 mmol/l) was analyzed for standard twice-per-day testing (before breakfast and dinner). In the second, detection was analyzed for four-times-per-day testing (before all meals and at bedtime). These results show that the sensitivity (TPF) is 14 and 39% for twice-per-day and four-times-per-day testing, respectively. There are no FPs in

this analysis because the blood glucose values are assumed to be true.

In contrast, the biographer with an alert level of 4.4 mmol/l has a 42% TPF, with only a 3% FPF (see table inserted in Fig. 2). Thus, even with a less than optimal choice for the low-glucose alert level, the biographer detects more hypoglycemic events than four blood glucose measurements per day, with few FPs. Moreover, the biographer exceeds the detection obtained with two blood glucose measurements per day. Given that the majority of patients with type 1 diabetes measure blood glucose values two or fewer times per day (13), the biographer provides an important improvement over current medical practice.

The area under the ROC curve is often used to judge the value of a diagnostic test. An ideal test would have an area under the curve (AUC) of 1.0. A test with AUC <0.5 has little diagnostic utility. For example, Meloy et al. (14) used a reflectance meter (Accu-chek III; Boehringer Mannheim, Indianapolis, IN) to determine hypoglycemia (defined as blood glucose <2.2 mmol/l) in newborns relative to a laboratory device. Their ROC analysis showed an AUC of ~0.85 for measurements made within 1 h of birth. Boyd (15) discusses the use of parathyroid hormone (PTH), phosphate ion (PO_4^-), and chloride ion (Cl^-) to differentiate patients with primary hyperthyroidism (confirmed by biopsy) from healthy subjects. The ROC analysis showed AUC of 0.98, 0.84, and 0.54 for PTH, PO_4^-, and Cl^-, respectively. Thus, PTH has high diagnostic utility, whereas Cl^- has little value. For the home-environment study presented here, an AUC value of 0.91 was obtained, indicating high diagnostic utility.

It might be argued that the definition of hypoglycemia (blood glucose ≤3.9 mmol/l) used in this analysis is higher than that commonly associated with symptoms in many patients. The specific definition of hypoglycemia is somewhat arbitrary. The more important issue is the difference between the definition of hypoglycemia and the selected low-glucose alert level. The implication of this analysis is that the biographer's low-glucose alert level should be set conservatively relative to the actual level of concern for a given patient. Specifically, setting the low-glucose alert from 1.1 to 1.7 mmol/l above the problem level for the patient is likely to optimize the trade-off between TPF and FPF.

In conclusion, the GlucoWatch biographer, after a single blood glucose measurement for calibration, provides 12 h of frequent (3/h) and automatic glucose readings. The frequent and automatic nature of the readings allows for more effective detection of hypoglycemia than that achieved with current medical practice, with a minimal amount of FPs. In addition, it provides low-glucose alert levels that can be adjusted to the patient's need to achieve a higher detection frequency at the expense of additional FP readings. Moreover, by checking previous biographer readings (trend analysis) and evaluating the specific situation, the patient can decide whether action is needed once the alarm sounds.

This device holds great promise in becoming an important tool to help patients aggressively manage diabetes while avoiding or reducing the incidence of severe hypoglycemia. Further studies should be performed to document the ability of the biographer to improve these health outcomes. Additional development should be focused on methods to further improve the balance of TPF versus FPF and thus enable even more effective detection of hypoglycemia.

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