Rates of Glucose Change Measured by Blood Glucose Meter and the GlucoWatch Biographer During Day, Night, and Around Mealtimes

TIMOTHY C. DUNN, BS
RICHARD C. EASTMAN, MD
JANET A. TAMADA, PHD

OBJECTIVE — The purpose of this study was to characterize the distribution of the rate of change of blood glucose for a diabetic population.

RESEARCH DESIGN AND METHODS — The study population consisted of 124 adults with type 1 or type 2 diabetes requiring insulin. Study participants applied a GlucoWatch Biographer during the day at home for 5 consecutive days and took finger-prick blood glucose measurements hourly. Subjects kept a diary of meals. The Biographer frequently and automatically measured glucose up to three times per hour for up 12 h. Rates of glucose change were calculated for both Biographer and blood glucose measurements. Rates of glucose change during a separate study of 134 subjects were determined for daytime and nighttime use.

RESULTS — Mean (±SD) rates of change of glucose of -0.36 ± 0.95 and 0.36 ± 0.99 mg · dl^{-1} · min^{-1} were found before and after lunch using blood glucose data and -0.31 ± 1.23 and 0.43 ± 1.26 using Biographer data. For both types of diabetes, rates of glucose change exceeded 2 mg · dl^{-1} · min^{-1} before and after meals ~10% of the time. Periprandial glucose patterns showed some significant differences between type 1 and type 2 diabetic subjects. Glucose levels changed more gradually at night than during the day.

CONCLUSIONS — Glucose values were almost equally unstable before and after meals. Glycemic instability around dinner was different in type 1 and type 2 diabetes. The GlucoWatch Biographer was found to be effective in tracking trends in glucose levels and yielded similar results as obtained by finger-prick blood samples.

Diabetes Care 27:2161–2165, 2004

Frequent glucose monitoring is an essential component of an intensive glycemic control regimen (1), but compliance is difficult due to the inconvenience of conventional skin-prick blood glucose testing. The GlucoWatch G2 Biographer (Cygnus, Redwood City, CA) is a device that provides the user with glucose measurements frequently and automatically (2–5). The Biographer samples glucose transdermally by application of a low-level electric current across the skin, a technique known as reverse iontophoresis (6–8). An in situ biosensor uses electrochemical detection to measure the amount of glucose extracted.

Little has been published on the rate of glucose change during normal daily activities, in part because of the difficulty in obtaining sufficient information using conventional glucose monitoring technology. The rate of glucose change may have importance in treatment decisions. For example, a measurement in the low end of the normal range is of little concern if the glucose level is flat or increasing, but may indicate impending hypoglycemia if the glucose level is rapidly decreasing. The rate of glucose change can affect alternative site blood glucose testing. Significant differences between finger and arm blood glucose values have been noted when glucose changed rapidly (9–11). Alternative site testing is recommended for use primarily before meals or >2 h after meals, when it is thought that glucose changes will be gradual.

The frequent measurements provided by the Biographer make it a useful tool to study rates of glucose change. The Biographer measures glucose obtained from interstitial fluid in the epidermis, where dynamics follow blood glucose closely, albeit with possible slight differences due to metabolism and transport effects (12). In this investigation, rates of glucose change in diabetic subjects undergoing normal eating, insulin dosing, and activity patterns were investigated using measurements from conventional blood glucose testing on the fingertip and from the Biographer. Rates of glucose change around mealtimes were analyzed in detail using data from both devices.

RESEARCH DESIGN AND METHODS

— The data from two clinical studies, one home-use study and one simulated home-use study, were analyzed by frequency distribution of rates of glucose change to characterize glycemic stability in an insulin-using diabetic population. The studies used a first-generation GlucoWatch Biographer, which provided up to three readings per hour for up to 12 h after a 3-h warm-up. Performance of the Biographer compared with blood glucose samples in these studies has been previously reported (13).

The simulated home-use study consisted of 134 subjects across six clinical

From Cygnus, Redwood City, California.
Address correspondence and reprint requests to Richard C. Eastman, MD, Cygnus, 400 Penobscot Dr., Redwood City, CA 94063. E-mail: reastman@cygn.com.
Received for publication 2 February 2004 and accepted in revised form 13 May 2004.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

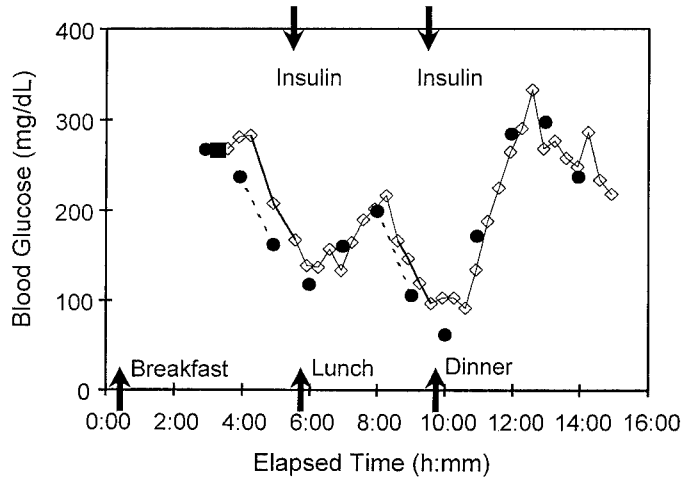

Figure 1—*Profile of a subject showing rate of glucose change before meals by blood glucose meter and Biographer measurements.* ●*, blood glucose meter;* ◇*, Biographer;* ■*, calibration point; – –, rate of change of blood glucose before meals; —, rate of change of Biographer glucose before meals.*

sites. The mean age was 48.4 ± 12.1 years ([mean ± SD], range 20–75), 87 (65%) were women and 47 (35%) men, 115 (85.8%) were Caucasian, 16 (12%) African American, 1 (0.7%) Asian, 1 (0.7%) Hispanic, and 1 (0.7%) categorized as other. Seventy-three (55%) subjects had type 1 diabetes and 61 (45%) type 2, with a mean duration of diabetes of 17.5 ± 10.5 years (range 1.5–45.7). The subjects wore Biographers for two daytime uses and one nighttime use at the clinical site. Measurements were taken from ~9:00 A.M. to 9:00 P.M. during the day and 9:30 P.M. to 6:30 A.M. at night. Subject diet and activities were not restricted to simulate normal daily life as much as possible. Blood glucose measurements were taken twice per hour (one 20- and one 40-min interval) using a HemoCue (Aktiebolaget Leo, Helsingborg, Sweden) photometer blood glucose analyzer for 12 h during the daytime periods.

In the home-use study, the population consisted of 124 subjects across six clinical sites. The mean age was 46.5 ± 11.7 years (range 18–75), 78 (63%) were women and 48 (37%) men, 99 (79.8%) were Caucasian, 11 (8.9%) African American, 9 (7.3%) Hispanic, and 5 (4.5%) categorized as other. Seventy-four (59.7%) had type 1 diabetes and 50 (40.3%) had type 2 diabetes, with a mean duration of disease of 16.9 ± 10.2 years (range 1.6–42.7). Subjects were trained on Biographer and blood meter use. They wore the Biographers for five daytime periods at home or work and took blood glucose measurements once per hour from the finger using a OneTouch Profile blood glucose meter (LifeScan, Milpitas, CA). Subjects recorded meals in a daily diary.

For the home-use study, information from the subject's self-reported typical insulin injection regimens was used to divide the population into three treatment groups. The "regular" group used regular insulin alone or in addition to an intermediate- or long-acting insulin or pump. The "fast" group used fast-acting insulin (lispro) plus a basal pump or intermediate- or long-acting insulin. The "long" group used intermediate- or long-acting insulin only.

The rate of glucose change was calculated for each measurement from the Biographer or blood glucose meter by using the current and previous reading, up to 2 h prior if there were missing readings. For the analysis of glycemic stability around mealtimes, preprandial was defined as 0–60 min before mealtimes and postprandial was defined as 30–90 min after mealtimes. Because of the study design, few measurements occurred around breakfast, and data were analyzed around lunch and dinner. To examine the significant factors in the observations of the rate of change of blood glucose around mealtimes, linear least-squares models of the data were evaluated using JMP (version 5.0.1.2; SAS Institute, Cary, NC). In the first analysis, four main effects (meal, period, diabetes type, and device) and all first-order cross terms were included in the model. In a second analysis, the premeal and postmeal data were evaluated separately to determine differences in rates of glucose change before and after lunch and dinner for type 1 and type 2 diabetic subjects. For this analysis, a linear least-squares model was evaluated with three main effects (meal, diabetes type, and device) and all first-order cross terms. A third linear least-squares model examined the effect of insulin injection regimens on the observations of the rate of change of blood glucose, with the pre- and postmeal periods analyzed separately. The four main effects of meal, diabetes type, device, and treatment regimen were used in the model. The Tukey test was used for all multiple comparison procedures, and statistical significance was defined as $P < 0.05$.

RESULTS — Figure 1 shows an example finger-prick blood and Biographer glucose profile for a subject during home use of the device. The Biographer was calibrated at 3 h with the blood glucose reading from the meter. The Biographer was applied at ~7:00 A.M., and lunch and dinner were consumed at ~6 and 11 h of elapsed time, respectively. The rate and direction of glucose levels changed throughout the day, corresponding to when mealtimes occurred.

Usable data on rates of glucose change were available from 120 of the subjects for the simulated home-use study and 111 subjects for the home-use study (Table 1). For the simulated home-use study, rates in excess of 3 mg · dl^{-1} · min^{-1} both upward and downward were observed in >2% of observations, and rates >2 mg · dl^{-1} · min^{-1}, both upward and downward, were observed ~8% of the time for both Biographer and blood glucose data. For the home-use study, the rate distribution measured by Biographer was similar to that of the simulated home-use study, but rates measured by blood glucose were slower. The Biographer data distribution pattern for the simulated home-use study at night indicated that glucose profiles underwent less rapid change at night than during the day. Mean values for the rate of change were close to zero in all cases. The SD of the rate of change was similar for the Biographer and blood glucose measurements for the simulated home-use study (1.17 and 1.19 mg · dl^{-1} · min^{-1}, respectively) and for the Biographer measurements for the home-use study (1.22 mg · dl^{-1} · min^{-1}). The

Table 1—*Distribution of rates of glucose change in two diabetic subject populations*

	Home use		Simulated home use		
	Finger-prick blood (day)	Biographer interstitial (day)	Finger-prick blood (day)	Biographer Interstitial	
				Day	Night
Rate of change (mg · dl^{-1} · min^{-1})					
≤3	0.2	1.3	1.4	1.1	0.6
−3 to −2	1.4	3.7	2.4	3.9	1.5
−2 to −1	9.1	12.7	13.1	12.9	8.8
−1 to 0	45.5	34.5	41.0	36.8	43.7
0 to 1	32.1	31.4	27.4	30.4	36.5
1 to 2	9.6	11.6	10.8	10.4	7.3
2 to 3	1.9	3.5	2.8	3.2	1.3
>3	0.3	1.3	1.2	1.1	0.4
Mean ± SD	−0.04 ± 0.95	−0.02 ± 1.22	−0.09 ± 1.19	−0.07 ± 1.17	−0.07 ± 0.91
Number of data points	4,819	10,743	3,767	5,835	2,057
Number of subjects	111	111	120	120	119

Data are percent, unless noted otherwise.

SD of the rate of change was lower for the blood measurements for the home-use study (0.95 mg · dl^{-1} · min^{-1}). The Biographer measurements during the night also showed lower SDs, indicating greater stability in glucose profiles (0.91 mg · dl^{-1} · min^{-1}).

For the finger-prick method, the magnitudes of the mean rates of change pre- and postlunch were found to be identical, at 0.36 mg · dl^{-1} · min^{-1} (Table 2). The SDs of the glucose rates of change were 0.95 and 0.99 mg · dl^{-1} · min^{-1} pre- and postlunch, respectively. Similar trends were found around dinner, although the decrease before dinner (−0.18 mg · dl^{-1} · min^{-1}) tended to be lower than the increase after dinner (0.25 mg · dl^{-1} · min^{-1}). The Biographer measurements showed similar means and higher SDs compared with the blood glucose data. For example, mean (±SD) rates of −0.36 ± 0.95 and 0.36 ± 0.99 mg · dl^{-1} · min^{-1} were found for pre- and postlunch for the finger-prick method for all subjects, compared with −0.31 ± 1.23 and 0.43 ± 1.26, respectively, for the Biographer.

A distribution analysis of the Biographer data indicated 8.7% of the glucose readings decreased more rapidly than 2 mg · dl^{-1} · min^{-1} prelunch and 8.8% of readings increased >2 mg · dl^{-1} · min^{-1} postlunch. Thus the Biographer confirmed the finding that pre- and postprandial changes in glucose levels were similar, but opposite in sign. Around dinner, 6.0% of readings decreased and 8.1% of readings increased >2 mg · dl^{-1} · min^{-1}, before and after dinner, respectively. In absolute value, rates of glucose change exceeded 2 and 3 mg · dl^{-1} · min^{-1} 11.8 and 3.1% of the time before lunch, respectively, and 12.0 and 3.2% after lunch, respectively. In absolute value, 8.9 and 2.2% of readings before dinner and 12.7 and 4.4% of readings after dinner, exceeded 2 and 3 mg · dl^{-1} · min^{-1}, respectively.

The ANOVA of the least-squares model of glucose rate of change with de-

Table 2—*Rates of glucose change in blood and interstitial fluid before and after meals*

	Finger-prick blood glucose			Biographer interstitial glucose		
	All	Type 1 diabetes	Type 2 diabetes	All	Type 1 diabetes	Type 2 diabetes
Before lunch						
Number of data points	433	280	153	874	583	291
Mean ± SD	−0.36 ± 0.95	−0.37 ± 1.01	−0.35 ± 0.84	−0.31 ± 1.23	−0.29 ± 1.26	−0.34 ± 1.18
After lunch						
Number of data points	410	269	141	894	611	283
Mean ± SD	0.36 ± 0.99	0.38 ± 0.98	0.33 ± 1.00	0.43 ± 1.26	0.46 ± 1.30	0.38 ± 1.15
Before dinner						
Number of data points	403	261	142	860	565	295
Mean ± SD	−0.18 ± 0.79	−0.23 ± 0.84	−0.09 ± 0.66	−0.12 ± 1.16	−0.18 ± 1.15	0.01 ± 1.16
After dinner						
Number of data points	345	225	120	830	547	283
Mean ± SD	0.25 ± 0.95	0.20 ± 0.99	0.36 ± 0.85	0.26 ± 1.31	0.22 ± 1.31	0.34 ± 1.33

Rate of change results are in units of mg · dl^{-1} · min^{-1}.

Table 3—*Effect of an insulin injection regimen on the rate of glucose change*

	Type 1 diabetic groups			Type 2 diabetic groups		
	Regular	Fast	Long	Regular	Fast	Long
Number of patients	33	31	5	25	7	10
Finger-prick blood glucose						
Before lunch						
Number of data points	119	137	24	89	23	41
Mean ± SD	−0.34 ± 0.87	−0.36 ± 1.04	−0.60 ± 1.42	−0.37 ± 0.80	−0.60 ± 0.78	−0.17 ± 0.93
After lunch						
Number of data points	117	130	22	83	23	35
Mean ± SD	0.34 ± 0.89	0.44 ± 1.08	0.21 ± 0.85	0.29 ± 1.04	0.49 ± 1.03	0.31 ± 0.88
Before dinner						
Number of data points	124	121	16	86	23	33
Mean ± SD	−0.24 ± 0.90	−0.23 ± 0.84	−0.15 ± 0.39	−0.08 ± 0.70	−0.04 ± 0.62	−0.14 ± 0.56
After dinner						
Number of data points	108	101	16	72	16	32
Mean ± SD	0.17 ± 0.99	0.20 ± 1.01	0.40 ± 0.97	0.37 ± 0.92	0.54 ± 0.65	0.22 ± 0.77
Biographer interstitial glucose						
Before lunch						
Number of data points	246	292	45	166	57	68
Mean ± SD	−0.24 ± 1.28	−0.35 ± 1.19	−0.20 ± 1.51	−0.33 ± 1.19	−0.41 ± 0.98	−0.33 ± 1.32
After lunch						
Number of data points	258	309	44	166	53	64
Mean ± SD	0.45 ± 1.26	0.50 ± 1.31	0.24 ± 1.49	0.35 ± 1.20	0.49 ± 1.19	0.36 ± 0.97
Before dinner						
Number of data points	248	273	44	176	48	71
Mean ± SD	−0.24 ± 1.12	−0.18 ± 1.20	0.11 ± 0.98	0.05 ± 1.24	−0.11 ± 1.15	−0.01 ± 0.94
After dinner						
Number of data points	252	256	39	175	52	56
Mean ± SD	0.15 ± 1.39	0.31 ± 1.25	0.07 ± 1.03	0.24 ± 1.27	0.58 ± 1.41	0.45 ± 1.41

Rate of change results are in units of mg · dl^{-1} · min^{-1}.

vice, period, meal, and diabetes type as parameters found that the device, Biographer or blood glucose meter, was not a significant factor in measuring glucose rate of change, confirming that the two devices provided similar information on glycemic profiles. The period (pre- or postmeal) was significant, as glucose generally decreased before meals and increased after meals. Two interactions were found to be significant effects: diabetes type and meal ($P = 0.0025$) and meal and period (pre- or postmeal) ($P < 0.0001$).

Interaction effects of diabetes type and meal were investigated in more detail in the second model, which divided the data into pre- and postmeal periods. For both the premeal ($n = 2,570$) and the postmeal ($n = 2,479$) data subsets, the model fit the data with high levels of significance ($P < 0.0001$ and $P = 0.015$, respectively). Examination of interaction effects revealed that type 2 diabetic subjects declined more rapidly prelunch compared with predinner, whereas type 1 diabetic subjects showed similar decreases before lunch and dinner. Type 1 diabetic subjects rose more rapidly after lunch than dinner, whereas type 2 diabetic subjects showed similar increases postlunch and postdinner. Type 1 and type 2 diabetic subjects showed similar declines prelunch and similar increases postlunch. Type 1 diabetic subjects declined more rapidly before dinner compared with type 2 diabetic patients. After dinner, type 1 and type 2 diabetic subjects increased similarly.

Examination of the effect of insulin injection regimen in the third model found that for the premeal data subset ($n = 2,570$) only the effect of meal was found to be significant ($P < 0.0001$), with decreases before lunch being more than twice the rate of decline before dinner (Table 3). No differences between the insulin injection regimen groups were found to be significant. For the postmeal data subset ($n = 2,479$), the model fit the data with a high level of significance ($P = 0.0036$). The effects of meal and treatment group were found to be significant ($P = 0.0017$ and $P = 0.038$, respectively). Rates of glucose increase after lunch were found to be almost twice those after dinner. The posttest on the treatment groups found that the fast group had a significantly higher average rate of glucose increase after meals (0.42 mg · dl^{-1} · min^{-1}) compared with the regular group (0.29 mg · dl^{-1} · min^{-1}), but was not significantly different from the long group (0.28 mg · dl^{-1} · min^{-1}), probably due to the small sample size in the long group.

CONCLUSIONS — From the glucose profiles observed in these studies, it can be seen that glucose measurements taken before mealtimes, or even seven times daily, would not be able to capture the dynamics that occur in glucose levels. Data from >100 insulin-using subjects indicated that rapid glucose changes can

occur at any time, even preprandially, with a fairly high frequency. The type 1 and type 2 diabetic populations showed overall similar patterns, and both showed glucose changes in excess of 2 $mg \cdot dl^{-1} \cdot min^{-1}$, both pre- and postprandially, ~10% of the time. At night the changes in blood glucose were more gradual than during the day, with <4% of measurements >2 $mg \cdot dl^{-1} \cdot min^{-1}$.

The Biographer gave identical conclusions of glycemic stability as the blood glucose readings. For the home-use study, the Biographer data showed larger SDs in the rate of change than the blood glucose data, but for the simulated home-use study, SDs were similar. The difference in SDs between devices for the home-use study can be attributed to the greater frequency of readings (up to every 20 min in this study) for the Biographer compared with the hourly blood glucose readings. For the simulated home-use study, where blood glucose readings were taken twice per hour, the distribution of rates of change was similar between blood glucose and Biographer data. Therefore, it is evident that a higher reading frequency detected rapid glucose changes more readily. Physiologically significant changes occur in time periods of <1 h, so the higher frequency measurements may give a better picture of the rate of glucose changes. The data in this analysis were obtained from the GlucoWatch Biographer, the first-generation device. The second-generation device, the GlucoWatch G2 Biographer, gives more frequent measurements (up to six per hour) for up to 13 h after calibration. This may allow even better profiles of glycemic rates of change.

It was beyond the scope of this study to determine the reasons for differences in glycemic stability in subjects with different types of diabetes. These differences could be due to unexamined differences in insulin injection or differences in meal composition and/or timing with injections or other factors such as exercise. Additional studies controlling for these variables would be of interest.

Current insulin dosing rules are based on single blood glucose determinations at critical times, such as before meals and bedtime, and in some cases after meals. Biographer users will have additional information available to them at the time they are making these decisions. They will be able to see whether their glucose is stable, rising, or falling. The availability of this data will likely challenge patients and providers to learn to deal with the added information. Decisions around the timing of insulin dosing and meals might be affected by knowledge that the glucose level is stable, falling, or rising rapidly. Since there are no existing rules to guide patients or providers on the use of this type of data, studies are urgently needed to develop treatment guidelines that encompass the additional data that are available from frequent glucose monitors.

References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Tamada JA, Garg SK, Jovanovic L, Fermi S, Potts RO, Cygnus Research Team: Noninvasive glucose monitoring: comprehensive clinical results. *JAMA* 282:1839–1844, 1999
3. Garg SK, Potts RO, Ackerman NR, Fermi SJ, Tamada JA, Chase HP: Correlation of fingerstick blood glucose measurements with GlucoWatch Biographer glucose results in young subjects with type 1 diabetes. *Diabetes Care* 22:1708–1714, 1999
4. Eastman RC, Chase HP, Buckingham B, Hathout EG, Fuller-Byk L, Leptien A, Van Wyhe MM, Davis TL, Fermi SJ, Pechler H, Sahyun G, Lopatin M, Wang BY, Wei C, Bartkowiak M, Ginsberg BH, Tamada JA, Pitzer K: Use of the GlucoWatch biographer in children and adolescents with diabetes. *Pediatr Diabetes* 3:127–134, 2002
5. Tierney MJ, Tamada JA, Potts RO, Jovanovic L, Garg S, Cygnus Research Team: Clinical evaluation of the Gluco Watch Biographer: a continual, non-invasive glucose monitor for patients with diabetes. *Biosens Bioelectron* 16:621–629, 2001
6. Glikfeld P, Hinz RS, Guy RH: Noninvasive sampling of biological fluids by iontophoresis. *Pharm Res* 6:988–990, 1989
7. Rao G, Glikfeld P, Guy RH: Reverse iontophoresis: development of a noninvasive approach for glucose monitoring. *Pharm Res* 10:1751–1755, 1993
8. Tamada JA, Bohannon NJV, Potts RO: Measurement of glucose in diabetic subjects using noninvasive transdermal extraction. *Nat Med* 1:1198–1201, 1995
9. Jungheim K, Koschinsky T: Glucose monitoring at the arm: risky delays of hypoglycemia and hyperglycemia detection. *Diabetes Care* 25:956–960, 2002
10. Ellison JM, Stegman JM, Colner SL, Michael RH, Sharma MK, Ervin KR, Horwitz DL: Rapid changes in postprandial blood glucose produce concentration differences at finger, forearm, and thigh sampling sites. *Diabetes Care* 25:961–964, 2002
11. Fineberg SE, Bergenstal RM, Bernstein RM, Laffel LM, Schartz SL: Use of an automated device for alternative site blood glucose monitoring. *Diabetes Care* 24: 1217–1220, 2001
12. Kulcu E, Tamada JA, Reach G, Potts RO, Lesho MJ: Physiological differences between interstitial glucose and blood glucose measured in human subjects. *Diabetes Care* 26:2405–2409, 2003
13. Tierney MJ, Tamada JA, Potts RO, Eastman RC, Pitzer K, Ackerman NR, Fermi SJ: The GlucoWatch Biographer: a frequent, automatic and non-invasive glucose monitor. *Ann Med* 32:632–641, 2000