Ambulatory Glucose Profile: Representation of Verified Self-Monitored Blood Glucose Data

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Sixty-nine individuals with diabetes (23 with type I, 15 with pregestational, and 31 with gestational) used specially modified reflectance meters containing memory chips enabling the instruments to store 440 individual blood glucose values with corresponding time and date. These data were organized into 14-day periods and then collapsed into a graphic depiction, the Ambulatory Glucose Profile (AGP), which was represented as the pattern of the 25th, 50th, and 75th percentiles of blood glucose values. These three curves illustrate the median level of control and provide an index of variability in control at each hour of a "typical day."

We observed distinctive AGPs related to the variability in metabolic control and the type of diabetes. Comparisons between diagnostic groups showed consistent differences between groups, independent of level of glycemic control. Review of serial AGPs obtained for sequential 2-wk periods for 23 nonpregnant individuals with type I diabetes and 10 women with gestational diabetes revealed changes in AGP corresponding to alterations in regimen.

The AGP provides a new approach to the evaluation of glycemic control, with applications to patient and physician education, clinical investigation, and individual patient care. *Diabetes Care* 10:111–17, 1987

The goal of improving metabolic control for individuals with diabetes has led to numerous technological advances. With specific reference to self-monitoring of blood glucose, rapid progress has moved diabetes management over the past decade from visually read glucose oxidase strips and cumbersome nonportable reflectance meters to miniaturized reflectance meters that are not only portable but accurate to within 5% of laboratory values (1–5). Even the most accurate and convenient of the reflectance meters, however, requires the maintenance of logbooks that are used by the person with diabetes and the physician to assess metabolic control and assist in decisions to alter diet, insulin, and/or exercise regimens.

Two major problems concerning the use of reflectance meters have recently surfaced, making their application as they are currently constituted less than optimal. First, the reliance on self-reported blood glucose values assumes a level of precision and reliability that has now been brought into serious question. Our own recent research, corroborated by other investigators (6–8), indicates that as many as 75% of the individuals using home blood glucose monitoring report data that are significantly different than their actual glucose values. Among type I individuals, we found patterns of inaccuracy and unreliability that produced apparent logbook glucose values significantly lower than true values. This resulted in serious omissions of chronic hyperglycemia that were often otherwise not apparent in glycosylated hemoglobin (HbA_1) or random glucose values determined in the laboratory. No set of physiologic or behavioral characteristics could be found to predict this behavior, nor could glycosylated hemoglobin be relied on to differentiate between verified and unverified data (9,10).

The second problem relates to the interpretation of capillary blood glucose data. In general, the physician currently scans the logbooks, searching for patterns or problems. The efficiency and reliability of this subjective method has not been sufficiently established and is probably quite variable. Recently, alternative systems of analyzing blood glucose values have been proposed to assist in both assessment and interpretation (11,12). Most of these systems rely on graphic displays developed by the patient who enters the glucose value as a point on a graph. The physician and/or patient reviews these graphic displays to see whether there are dis-

cernable patterns that in turn may assist in decisions concerning therapy. However, the efficiency of these methods, and therefore their practical use and utility in clinical decision making, is limited by the need for tedious repetitive construction of these graphic displays. Introduction of the computer has led to the development of software to facilitate and expedite this process as well as provide advice, explanations, interpretations, and assist in evaluation of compliance (13). However, even with the computer to generate the graphics, a major impediment arises with regard to entry of data into the computer. Substantial errors can potentially occur in the transfer of data from the logbook to the computer. We describe how the use of a reflectance meter modified by the addition of a memory microchip led to the development of a systematic approach to representing and interpreting capillary blood glucose data.

METHODS AND MATERIALS

Subjects. Data for this study were derived from participants in previous and current investigations. These included individuals with type I diabetes already participating in a study to determine the efficacy of intensive treatment regimens, women with pregestational diabetes (with type I or type II diabetes before pregnancy) who were referred for intensive insulin therapy to improve metabolic control during pregnancy, and pregnant women who had been screened and diagnosed between the 24th and 32nd wk of gestation as having gestational diabetes and subsequently referred for diabetes management. All subjects in these studies were taught how to test capillary blood glucose via an Autolet (Owen Mumford, Oxon, UK), to obtain an adequate blood sample, and to employ a glucometer (Ames Division, Miles, Elkhart, IN) to measure blood glucose. The subjects were placed on regimens involving multiple (up to 7) capillary blood glucose tests each day and were either prescribed insulin (a "split-mixed" regimen of short and intermediate acting) and diet (synchronized with insulin therapy) or diet only (for individuals with gestational diabetes whose glucose control rapidly responded to dietary intervention). All subjects were independently assessed for metabolic control with HbA_1 determinations carried out at 2-wk intervals (14).

To obtain accurate and reliable data, the subjects were given a recording memory glucose reflectometer. These were standard reflectance meters modified by the addition of a microchip that enabled the recording of 440 glucose values with corresponding time and date (6,15).

For evaluation, at 2-wk intervals, memory-meter data were transferred to an Apple IIe microcomputer (Apple, Cupertino, CA), an IBM PC, or an IBM XT (International Business Machines, White Plains, NY) providing patient-oriented data files. Standard outputs of the microcomputers include *1*) mean blood glucose for the period, *2*) mean glucose values by day of week, and *3*) mean glucose values by 4-h periods. Additionally, data could be displayed in various graphic formats to show the "typical" level of glycemic control (designated as the *modal day*) (15).

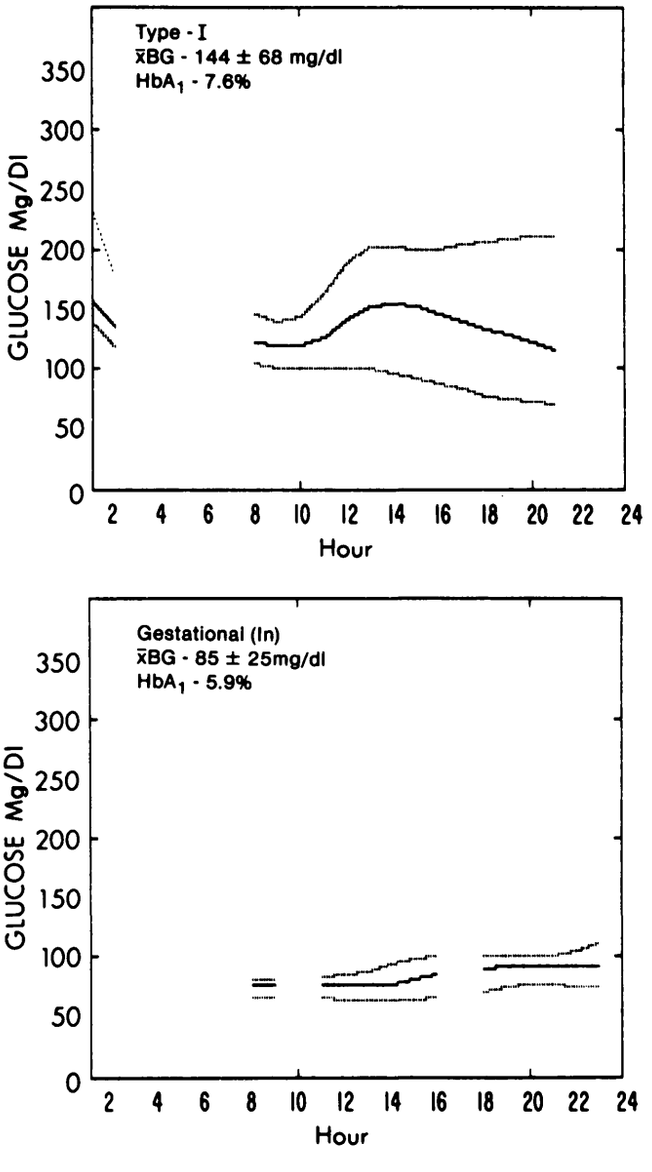

FIG. 1. Ambulatory glucose profile. *Vertical scale* shows capillary blood glucose (mg/dl); *horizontal scale* shows time of day on 24-h clock. Data were obtained via memory-equipped glucose reflectance meter over 2 wk. Data are combined as if they had all been obtained on 1 day. *Middle curve* shows median or 50th percentile, after appropriate smoothing. *Upper* and *lower curves* represent the 75th and 25th percentiles, respectively: 50% of glucose values will fall between *upper* and *lower curves*, and vertical distance between curves is interquartile range. Gaps appear when frequency of observations fall below minimal threshold [e.g., when sleeping, between 0200 and 0800 h (*top panel*), or when not tested, between 0900 and 1100 h and 1600 and 1800 h (*bottom panel*)].

Ambulatory glucose profile. Because information from the meter is entered into the computer as sequences of glucose values, each marked with the corresponding date and time, we were able to reformat the meter data to assist pattern

recognition and interpretation. With this system, the quality of glycemic control could be represented in terms of an ambulatory glucose profile (AGP) that selects capillary blood glucose data by 2-wk intervals and displays this information as if it occurred during a single typical day (Fig. 1). The 14-day interval was chosen because it usually provides enough data points to produce statistically stable estimates of the hourly values. Shorter (1-wk) or longer periods could be used if enough measurements are included and are spaced to cover fasting, preprandial, and postprandial periods. In our experience, a minimum of 60 readings is necessary to produce an AGP. This is based on four readings for each 1-h period between 0800 and 2300 h (the average waking hours).

The AGP is represented by three time series: the 25th, 50th, and 75th percentile glucose values (vertical scale) versus time of day (horizontal scale). These three curves depict the median level of glycemic control and an index of the variability in control for each hour for all of the days included in the glucose-profile period. Because there is variability in the number of measurements that fall within each 1-h interval and in the timing of the glucose determinations, each curve is subjected to smoothing to provide a clearer picture of the general time course while reducing the influence of outliers and the effect of random-sampling variability (16). The procedure involves calculating the median glucose values for each hour (e.g., 0800–0859 h). Next, each of these values is replaced with a new smoothed value [$y(i)$], which is determined by calculating the median values for three transformations corresponding to the periods before, during, and after the actual glucose test. This new value reflects the alteration in blood glucose during the 2-h interval immediately before and after the original 1-h period according to the formula

$$y(i) = \text{median } [u,v,w]$$

$$u = \text{median } \{y(i-1), [3 \cdot y(i-1) - y(i-2)]/2, y(i)\}$$

$$v = \text{median } [y(i-1), y(i), y(i+1)]$$

$$w = \text{median } \{y(i+1), [3 \cdot y(i+1) - y(i+2)]/2, y(i)\}$$

The smoothing sequence is iterated until two successive passes over the data point result in a negligible change in the smoothed glucose values. To preserve local peaks in the data, the smoothing process is divided into two stages. After the first pass over the data with the smoothing procedure, residual values are extracted from the differences between the input data and the resultant smoothed value. These residuals are smoothed and added back to the initial smoothed values, and then the process is carried out again.

The resultant AGP represents only periods where at least four determinations have been made within each hour. In cases where this criterion is not met, a gap appears on all three smoothed curves (see Fig. 1). Because the AGP generally reflects only daytime testing, it usually begins between 0600 and 0800 h and ends between 2300 h and midnight. A 24-h profile would be possible, in principle, if the patient were to test throughout the night, obtaining at least four determinations for each hour during a 2-wk period.

Interpretation of ambulatory glucose profile. The AGP may facilitate systematic interpretation of SMBG data in terms of the following questions: *1*) What is the overall level of glycemic control in terms of median glucose value? 2) What is the adequacy of patient self-monitoring with respect to the number of measurements and their distribution throughout the 24-h period? Which times of day have not been adequately checked? 3) What is the variability in glycemic control in terms of the "interquartile range" (the vertical distance between the 25th and 75th percentiles)? 4) What time of day shows the greatest problem for hypoglycemia in terms of a low median and/or 25th percentile? Which insulin dose (time and type) is primarily responsible for the glucose at this time of day? 5) Which time of day is the greatest problem with respect to hyperglycemia (high median and 75th percentiles), and which insulin (time and type) is primarily responsible for high blood glucose levels? 6) Are there any patterns? Is the profile flat? Are there excessive postprandial peaks? Are there upward or downward trends throughout the day or at night?

RESULTS

Data from three groups were evaluated (Table 1). Group 1 consisted of 23 subjects (7 men, 16 women) with type I diabetes who completed 8 wk of monitoring. The first 2 wk

TABLE 1

	Group 1, nonpregnant type I (N = 23)	Group 2, pregestational (N = 15)	Group 3, gestational (N = 31)
Mean age (yr)	26 ± 7	28 ± 5	30 ± 6
Mean duration of diabetes (yr)	12 ± 9	5 ± 3	N/A
Regimen	2–3 injections mixed insulin	2–3 injections mixed insulin	Mixed insulin and NPH at bedtime (25) Diet only (6)
Mean blood glucose (mg/dl)	159 ± 61	115 ± 45	91 ± 22
Mean number of tests (per day)	4.6 ± .8	6.5 ± 1.2	6.5 ± 1.2
Mean HbA_1 (%)	9.8 ± 2	7.7 ± 3	5.6 ± .8

Numbers in parentheses equal number of subjects.

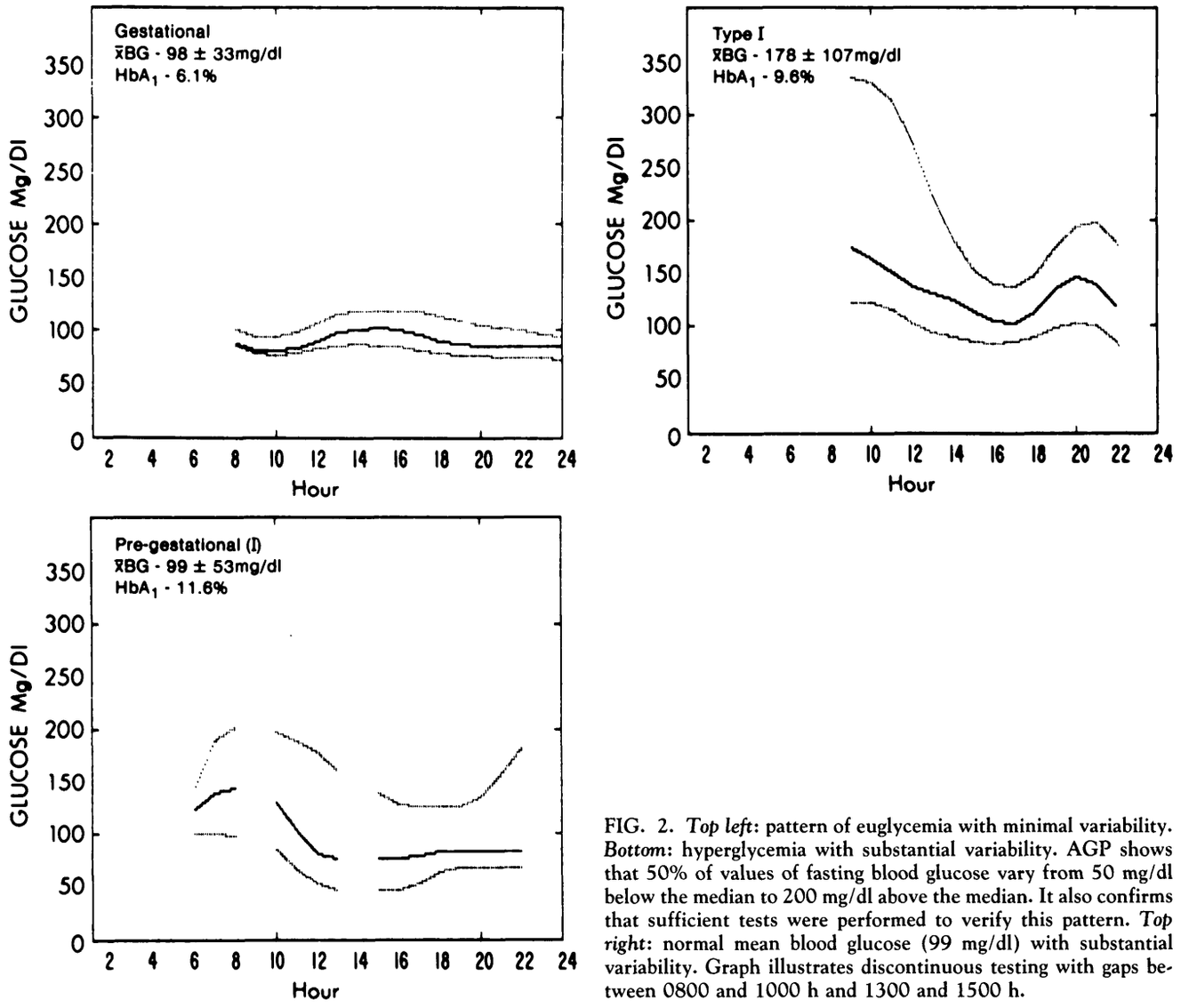

FIG. 2. *Top left*: pattern of euglycemia with minimal variability. *Bottom*: hyperglycemia with substantial variability. AGP shows that 50% of values of fasting blood glucose vary from 50 mg/dl below the median to 200 mg/dl above the median. It also confirms that sufficient tests were performed to verify this pattern. *Top right*: normal mean blood glucose (99 mg/dl) with substantial variability. Graph illustrates discontinuous testing with gaps between 0800 and 1000 h and 1300 and 1500 h.

served as a baseline interval during which no changes in regimen were made. This was followed by three 2-wk periods occurring within 3 mo of the initial baseline, during which changes in treatment were made. Throughout the study, group 1 participants tested an average of 4.6 ± 0.8 (SD) times per day. Group 2 consisted of 15 women with pregestational diabetes who completed only baseline-period monitoring. Group 3 consisted of 31 women with gestational diabetes of whom 10 continuously self-monitored from diagnosis (24–28 gestational wk) to delivery (38–42 gestational wk). Testing frequency for both pregestational and gestational subjects averaged 6.5 ± 1.2 (SD) times per day. Six individuals with gestational diabetes were on diet-only regimens. The remaining subjects were all placed on an insulin and diet regimen that consisted of two injections of mixed insulin (regular and NPH) with supplements of regular insulin before meals as needed.

Metabolic control for the nonpregnant subjects ranged from euglycemia (mean 80–120 mg/dl) to severe and chronic hyperglycemia (mean 250–330 mg/dl). For the individuals with pregestational or gestational diabetes, mean glycemic control ranged from 66–190 mg/dl.

We initially produced 248 2-wk AGPs for the 69 subjects, revealing several patterns in glycemic variation. Among these patterns, as illustrated in Fig. 2, were *1*) normal mean blood glucose with minimal variability, 2) normal mean blood glucose with substantial variability, and 3) high mean blood glucose with substantial variability. Most of the subjects in this investigation could be classified into these three categories. Patterns characterized as minimal variability with normal mean glucose appeared to occur throughout the day independent of the difference in level of control for any specific hour. The 25th and 75th percentile curves were approximately equidistant from the median throughout the

24-h period (Fig. 2, *top left*). In contrast, in patients with substantial variability (Fig. 2, *top right* and *bottom*), the 25th and 75th percentiles were less symmetrical around the median.

We next determined whether there was a significant difference between the AGPs produced by the nonpregnant type I group, the pregestational group, and the gestational group. We first characterized each patient's baseline 2-wk AGP ($N = 69$) by its four basic features: *1*) the grand mean for the 2-wk period, *2*) the average interquartile range, *3*) the number of reversals in the slope of the curve, and *4*) the average change in blood glucose value after a reversal. With these parameters, a multivariate analysis of variance was performed. The results showed an overall significant difference ($P = .003$) between the three groups, the type I diabetic group consistently producing the highest mean, the greatest interquartile range, and the largest average change after a reversal (Table 2). The pregestational and gestational groups were consistently second and third, respectively, for each of these dimensions. Individual univariate analyses carried out on the four parameters indicated that three parameters accounted for the significant overall multivariate effect: grand mean, interquartile range, and average change after a reversal. Pairwise comparisons for the grand mean indicated that the difference was significant by Sheffe's S procedure ($P < .05$) for comparisons between the type I diabetic group and the gestational and pregestational groups (Table 2). With respect to the interquartile range, the type I and gestational groups were significantly ($P < .05$) different from each other but not from the pregestational group. For the average changes after a reversal, the gestational group was significantly ($P < .05$) different than the other groups, which were not found to be significantly different from each other. Finally, no pairwise difference was found between groups for the number of reversals of the slope.

We then examined the AGPs for the 23 nonpregnant and 10 gestational subjects for whom data were available for a series of consecutive 2-wk intervals. Profiles were obtained for a baseline interval, during which there was no change in treatment, and for three to five follow-up 2-wk intervals. Sequential AGPs enabled evaluation of changes in metabolic control and patterns of testing. Figure 3 illustrates a set of AGPs encompassing the baseline and two follow-up periods for a 21-yr-old man with type I diabetes. Figure 3 (*top left panel*) depicts the initial 2 wk for which data were collected without any alteration in therapeutic regimen. The subject measured capillary blood glucose an average of 7 times/day (between 0800 and 1600 h and 1800 and 0200 h) and was on a regimen requiring short- and intermediate-acting insulins on awakening and before dinner. The AGP indicated rises in blood glucose after breakfast and dinner. An intervention plan combining caloric reduction with increased exercise was instituted immediately after the baseline interval. The *bottom panel* represents the first follow-up AGP produced 2 wk later. An overall reduction in mean blood glucose level, in variability, and in the level and duration of postprandial glucose excursions was noted after the first intervention period. By the next 2-wk period (4 wk after intervention) the AGP showed a significant improvement in the morning glucose excursions and a lowering of the midday glucose peaks.

TABLE 2
Comparison of Ambulatory Glucose Profile (AGP) characteristics for each diagnostic group

	Type I ($N = 23$)	Pregestational ($N = 15$)	Gestational ($N = 31$)
Mean AGP (mg/dl)	158.84	115.37	90.78
Mean interquartile range (mg/dl)	84.64	74.38	36.68
Reversals (N)	8.03	11.00	10.00
Change (mg/dl)	30.42	29.87	12.92

Multivariate analysis of variance was used to evaluate the difference between diagnostic groups simultaneously considering all parameters. Pairwise comparisons were made by Scheffe's S procedure.

Review of all 33 subjects for whom sequential AGPs were available showed that when improvement in overall metabolic control occurred (as measured by mean blood glucose), it was reflected in changes in the AGP. When no improvement occurred, the AGP was not found to have changed.

DISCUSSION

The AGP was developed to provide an accurate means of assessing glycemic control, to enable the patient and clinician to recognize patterns, and to facilitate clinical decision making. The memory meter utilizing validated data in conjunction with a microcomputer rapidly produced this graphic representation with several potential uses. First, it may be possible to determine whether individual patients show distinct patterns in terms of their AGP. Second, the effect of the type of diabetes and the impact of different therapies on patterns of ambulatory glycemic control may be more accurately evaluated. For example, the pregestational group (subjects with diabetes before pregnancy) appeared to have a different AGP than the nonpregnant subjects with type I diabetes. This may, however, have been due to the type of intensive treatment regimen and not to the nature of their metabolic disorder. Third, changes in metabolic control over time may be documented in the ambulatory patient. Fourth, in combination with other available computer outputs (e.g., mean, range, frequency of testing, and percentage of glucose values below, within, and above a target range) available in this system, the AGP may assist in providing overall assessment of glycemic control.

Several potential limitations concerning use of the AGP also need to be addressed. Other factors not directly reflected in the AGP (e.g., diet, insulin regimen, exercise, and stress) have a major impact on overall glycemic control but remain difficult to quantify, verify, record, and analyze. Additionally, frequent and sustained self-monitoring is needed to provide sufficient data to permit construction of the AGP. For example, because most patients cannot be expected to test capillary blood glucose at night, the AGP remains a

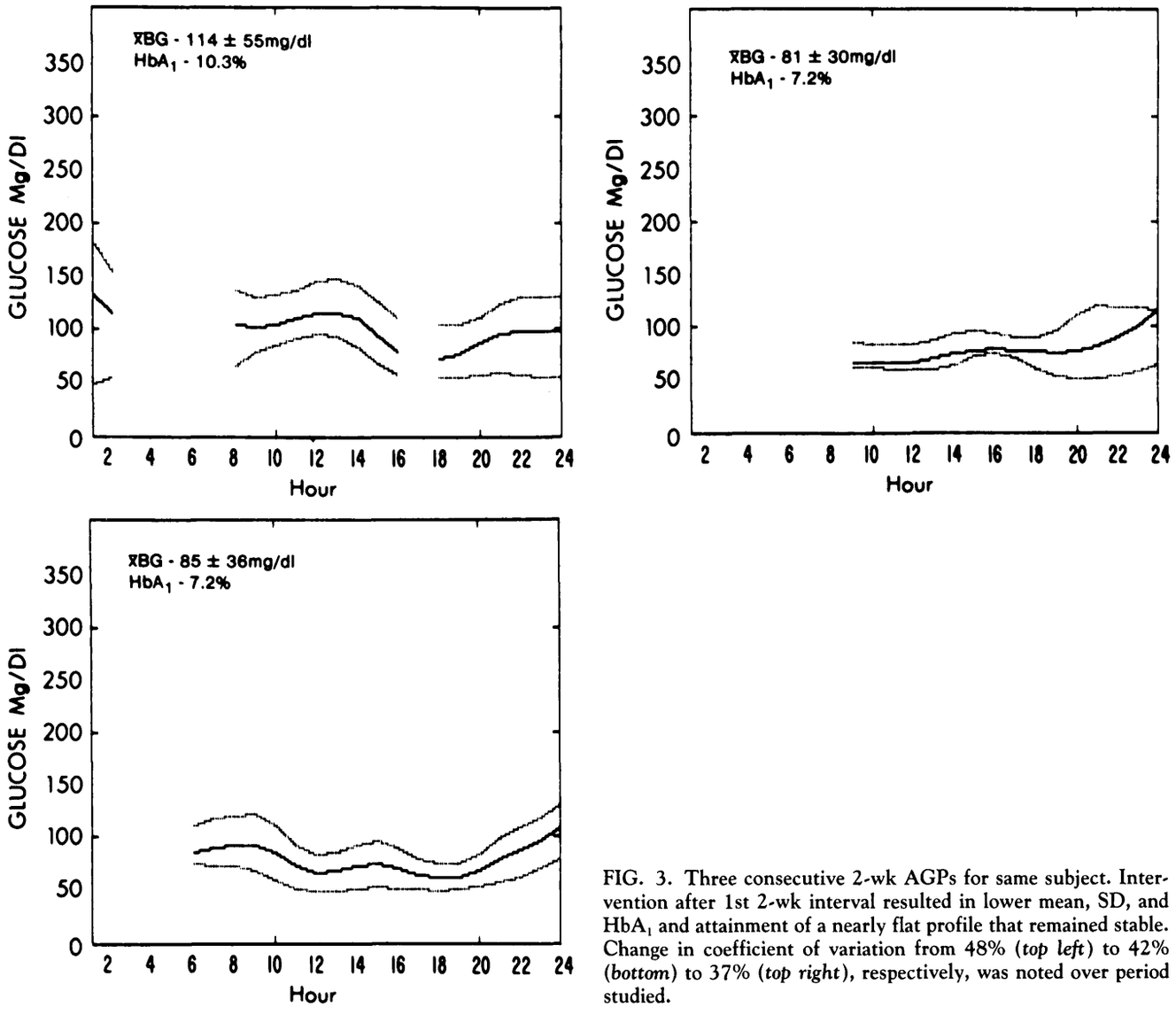

FIG. 3. Three consecutive 2-wk AGPs for same subject. Intervention after 1st 2-wk interval resulted in lower mean, SD, and HbA_1 and attainment of a nearly flat profile that remained stable. Change in coefficient of variation from 48% (*top left*) to 42% (*bottom*) to 37% (*top right*), respectively, was noted over period studied.

daytime profile (although in principle the method could analyze the 24-h circadian pattern). Furthermore, the smoothing and analysis process does not take into account the timing of meals. Similarly, because the AGP is not a continuous inpatient monitoring system (e.g., Biostator), it is subject to the limitations of individual patterns of testing in an ambulatory setting. For instance, if the subject tests consistently only in the morning during the 1st wk and the afternoon during the 2nd wk, the resulting pattern might not be representative. However, this would be readily uncovered by inspection of the tabular outputs from the electronic logbook that accompanies the AGP output. We found no case in which this artifact appeared. Finally, whether systematic use of the AGP per se may contribute to improved glycemic control remains unanswered. Our study was not intended to evaluate the efficacy of the AGP as the single factor for optimizing metabolic control. Whereas there was improvement in some individuals for whom sequential AGPs were produced, we also noted there were others whose AGP remained unaltered and whose metabolic control did not change. When improvement in control occurred, it might have been due to intensive involvement on the part of the patient and the health-care provider during the study period and not the AGP per se.

The AGP is a novel step in systematically presenting SMBG data and characterizing metabolic control. It reflects features of glycemic control beyond the simple mean blood glucose by graphically portraying the amplitude and frequency of changes in glycemic level, the characteristic glucose profile for a typical day, and the consistency, timing, and frequency of glucose testing. The information available from the AGP can potentially be used in practice for the

management of individual patients and as a means of answering research questions related to control and complications, the impact of new therapies, and the development, refinement, and testing of new algorithms for insulin adjustment.

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A computer program to construct the AGP is available for operation on the IBM-PC (256K RAM). Write to Dr. David Lucido, The DRTC Computer Laboratory, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

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REFERENCES

1. Ikeda Y, Tajima N, Ide Y, Yokoyama J, Abe M: Pilot study of blood glucose using the Dextrostix-Eyetone system for juvenile-onset diabetes. *Diabetologia* 15:91–93, 1978
2. Skyler JS, Lasky IA, Skyler DL, Robertson EG, Mintz DH: Home blood glucose monitoring as an aid in diabetes management. *Diabetes Care* 1:150–57, 1978
3. Sonkson PH, Judd SL, Lowy C: Home monitoring of blood glucose: method for improving diabetic control. *Lancet* 1:729–32, 1978
4. Tattersall RB: Home blood glucose monitoring. *Diabetologia* 16:71–74, 1979
5. Birch K, Halderbrandt P, Marshall MO, Sestoff L: Self-monitoring of blood glucose without a meter. *Diabetes Care* 4:414–16, 1981
6. Mazze R, Shamoon H, Pasmantier R, Lucido D, Murphy J, Hartmann K, Kuykendall V, Lopatin W: Reliability of blood glucose monitoring by patients with diabetes mellitus. *Am J Med* 77:210–17, 1984
7. Mazze RS, Pasmantier R, Murphy JA, Shamoon H: Self-monitoring of capillary blood glucose: changing the performance of individuals with diabetes. *Diabetes Care* 8:207–13, 1985
8. Wing RR, Lamparski DM, Zaslow S, Betschart J, Siminerio L, Becker D: Frequency and accuracy of self-monitoring of blood glucose in children: relationship to glycemic control. *Diabetes Care* 8:214–18, 1985
9. Langer O, Mazze R: Diabetes in pregnancy: evaluating self-monitoring performance and glycemic control with memory-based reflectance meters. *Am J Obstet Gynecol* 155:635–37, 1986
10. Shamoon H, Pasmantier R, Mazze R: Relation of glycosylated hemoglobin and blood glucose in patients with type I diabetes mellitus. *Am J Med* 80:1086–92, 1986
11. Bernstein RK: *Diabetes: The GlucograF Method for Normalizing Blood Sugar.* New York, Crown, 1981
12. Williams JR, Jr, Alling K: A program for normal glycemic control of insulin-dependent diabetes. *Diabetes Care* 3:160–62, 1980
13. Pernick NL, Rodbard D: Personal computer programs to assist with self-monitoring of blood glucose and self-adjustment of insulin dosage. *Diabetes Care* 9:61–69, 1986
14. Bunn HF: Evaluation of glycosylated hemoglobin in diabetic patients. *Diabetes* 30:613–17, 1981
15. Zimmet P, Gerstman M, Raper LR, Cohen M, Crosbie C, Kuykendall V, Michaels D, Hartmann K: Computerized assessment of self-monitored blood glucose results using a Glucometer(R) reflectance photometer with memory and microcomputer. *Diabetes Res Clin Pract* 1:55–63, 1985
16. Tukey JW: *Exploratory Data Analysis.* Menlo Park, CA, Addison-Wesley, 1977, p. 205–64