

1,5-Anhydroglucitol and Postprandial Hyperglycemia as Measured by Continuous Glucose Monitoring System in Moderately Controlled Patients With Diabetes

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OBJECTIVE— Postprandial hyperglycemia is often inadequately assessed in diabetes management. Serum 1,5-anhydroglucitol (1,5-AG) drops as serum glucose rises above the renal threshold for glucose and has been proposed as a marker for postprandial hyperglycemia. The objective of this study is to demonstrate the relationship between 1,5-AG and postprandial hyperglycemia, as assessed by the continuous glucose monitoring system (CGMS) in suboptimally controlled patients with diabetes.

RESEARCH DESIGN AND METHODS— Patients with type 1 or type 2 diabetes and an HbA_{1c} (A1C) between 6.5 and 8% with stable glycemic control were recruited from two sites. A CGMS monitor was worn for two consecutive 72-h periods. Mean glucose, mean postmeal maximum glucose (MPMG), and area under the curve for glucose above 180 mg/dl (AUC-180), were compared with 1,5-AG, fructosamine (FA), and A1C at baseline, day 4, and day 7.

RESULTS— 1,5-AG varied considerably between patients ($6.5 \pm 3.2 \mu\text{g/ml}$ [means \pm SD]) despite similar A1C ($7.3 \pm 0.5\%$). Mean 1,5-AG ($r = -0.45$, $P = 0.006$) correlated with AUC-180 more robustly than A1C ($r = 0.33$, $P = 0.057$) or FA ($r = 0.38$, $P = 0.88$). MPMG correlated more strongly with 1,5-AG ($r = -0.54$, $P = 0.004$) than with A1C ($r = 0.40$, $P = 0.03$) or FA ($r = 0.32$, $P = 0.07$).

CONCLUSIONS— 1,5-AG reflects glycemic excursions, often in the postprandial state, more robustly than A1C or FA. 1,5-AG may be useful as a complementary marker to A1C to assess glycemic control in moderately controlled patients with diabetes.

Diabetes Care 29:1214–1219, 2006

The importance of tight glycemic control in preventing the complications of diabetes has been well documented (1–3). More recently, studies indicate that postprandial glucose may be

an independent risk factor for the development of macrovascular complications (4–6). Many patients who are otherwise well controlled by HbA_{1c} (A1C), the current standard indicator of overall glyce-

mia, also have significant postprandial hyperglycemia (7). Currently, available markers for measuring glycemic control, including A1C and fructosamine (FA), only reflect average glucose, potentially missing important hyperglycemic excursions that may be balanced out by hypoglycemia. Therefore, an alternative marker that robustly reflects postprandial glucose excursions could be useful in the management of patients with diabetes.

Plasma 1,5-anhydroglucitol (1,5-AG) is a naturally occurring dietary polyol that has been proposed as a marker for postprandial hyperglycemia. An automated assay (Glycomark) has recently been approved in the U.S. as a short-term marker for glycemic control (8), and a similar assay has been in use in Japan for over a decade (9). During normoglycemia, 1,5-AG is maintained at constant steady-state levels due to a large body pool compared with the amount of intake (10) and due to a lack of metabolism (10,11). Normally, in the kidneys, 1,5-AG is filtered and completely reabsorbed (12). However, with elevated serum glucose concentrations (generally $>180 \mu\text{mol/l}$, the average renal threshold for glucose), glucose is not completely reabsorbed by the kidney, and serum 1,5-AG falls due to competitive inhibition of renal tubular reabsorption by glucose. The change in 1,5-AG depends on the duration and magnitude of glucosuria, and 1,5-AG recovers at a rate of $\sim 0.3 \mu\text{g} \cdot \text{ml}^{-1} \cdot \text{day}^{-1}$ when normoglycemia is restored. Thus, 1,5-AG responds sensitively and rapidly to changes in serum glucose, reflecting even transient elevations of glucose within a few days (13,14). 1,5-AG has been shown to reflect daily glycemic excursions in patients with A1Cs at or near goal (15). In contrast, A1C is an index of average glucoses over a much longer period of time (2–3 months), encompassing both hyperglycemia and hypoglycemia. A1C has been well validated through outcome studies as a surrogate marker of risk of both micro- and macrovascular complications. The characteristics of these

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Received for publication 7 October 2005 and accepted in revised form 21 February 2006.

J.L. holds stock in Medtronic MiniMed. E.A.B. is a paid consultant for Tomen America. S.W. has served on an advisory board for and has received honoraria and grant/research support from Medtronic MiniMed and has received honoraria from Tomen America.

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; AUC-180, area under the curve for glucose above 180 mg/dl; CGMS, continuous glucose monitoring system; FA, fructosamine; MPMG, mean postmeal maximum glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1910

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Table 1—Patient characteristics

Glycemic assays	Visit 1	Visit 2	Visit 3	Overall	Type 1	Type 2
A1C (%)	7.28 ± 0.63 (6.50–9.20)	7.29 ± 0.54 (6.50–9.10)	7.29 ± 0.57 (6.50–9.00)	7.29 ± 0.56 (6.53–9.10)	7.29 ± 0.47 (6.43–7.97)	7.30 ± 0.77 (6.53–9.10)
1,5-AG (μg/ml)	6.54 ± 3.5 (2.20–17.9)	6.83 ± 3.5 (2.30–17.4)	7.00 ± 3.6 (1.10–17.2)	6.79 ± 3.5 (1.87–17.5)	6.56 ± 3.0 (3.03–15.6)	7.34 ± 4.7 (3.43–17.5)
FA (μmol/l)	316 ± 45 (203–389)	320 ± 61 (198–537)	312 ± 46 (199–383)	316 ± 48 (200–424)	322 ± 50 (200–423)	301 ± 45 (231–349)
CGMS data						
Mean glucose (mg/dl)		148 ± 16 (109–174)			146 ± 17 (109–168)	152 ± 13 (142–174)
AUC-180 (mg · dl ⁻¹ · day ⁻¹)		13.5 ± 7.6 (1–27)			13.3 ± 7.3 (1–24)	13.8 ± 8.8 (4–27)
MPMG (mg/dl)		204 ± 40 (146–323)			204 ± 44 (146–323)	205 ± 30 (163–242)
Urinary glucose (g/day)				4.58 ± 5.5 (0.040–20.8)		

Data are means ± SD (range).

two assays suggest that 1,5-AG may be complementary to A1C with specific relevance to assessing postprandial hyperglycemia.

A continuous glucose monitoring system (CGMS) provides continuous recording of glucose levels (16–20), making it possible to examine the relationship between 1,5-AG and glycemic excursions, particularly with respect to postprandial hyperglycemia. This study examined the role of 1,5-AG as an assessment of patients who are in modest control, as reflected by A1C, in order to examine postprandial glycemic excursions.

RESEARCH DESIGN AND METHODS

Patients ($n = 40$) aged 18–75 years with type 1 or type 2 diabetes and an A1C between 6.5 and 8% with stable glycemic control were recruited from two university-affiliated diabetes clinics. Stable glycemic control was defined by patient recall, no recent addition of hypoglycemic medications or change in insulin dosing by >10% in the previous 3 months, and at least one A1C in the previous 6 months that varied by <0.5% from screening. To minimize the potential confounding effect of frequent glucose self-monitoring, patients must have already been checking glucoses at least twice daily (type 2) or three times daily (type 1). Exclusion criteria included pregnancy, severe medical illnesses, anemia, serum creatinine >2.0 mg/dl, or severe hypoglycemia requiring assistance in the previous 6 months.

A CGMS System Gold monitor (Medtronic MiniMed, Northridge, CA)

was worn for two consecutive 72-h periods and was used according to Food and Drug Administration–approved labeling. Its characteristics have been described elsewhere (16–20). Patients checked seven-point fingerstick glucose profiles before meals, 2 h after meals, and at bedtime and were taught how to enter them into the CGMS. A OneTouch Ultra glucose meter (Lifescan) was used in the majority of patients. A subset of patients also entered meal times into the CGMS. They were asked not to change their daily habits, particularly insulin administration, in response to the more frequent testing. Data were downloaded at the end of each 72-h interval and analyzed using Mini-Med Solutions software.

Serum 1,5-AG, A1C, and FA were checked on days 1, 4, and 7. A 24-h urine for glucose and creatinine was obtained on day 3. All assays were conducted by Esoterix (Calabasas Hills, CA). A1C was measured via high-performance liquid chromatography and FA via colorimetric assay. 1,5-AG was measured using an enzymatic colorimetric assay (Glycomark; Tomen America, New York, NY). The normal range for A1C is 4.2–5.9%, 1,5-AG 10.7–32.0 μg/ml, and FA <285 μmol/l.

Mean glucose was determined using the CGMS software with correction for incomplete data collection. The area under the curve for glucose above 180 mg/dl (AUC-180) (expressed as mg · dl⁻¹ · day⁻¹) was also determined by CGMS software and is a measure of the total area of glucose excursions above 180 mg/dl calculated for each 72-h period and for

the conglomerate 6-day study period. Mean postmeal maximum glucose (MPMG) is the mean maximal glucose value of postmeal glucose excursion after breakfast, lunch, or dinner, as determined by CGMS software. Not all patients entered meal makers into CGMS; therefore, MPMG was determined in a subset of patients. Mean 1,5-AG, A1C, or FA was determined using values from three study visits over 7 days.

The primary outcomes measure was the correlation between AUC-180 and mean 1,5-AG compared with mean A1C or FA. Secondary outcomes examined correlations between total or 72-h CGMS interval AUC-180 and mean or end-interval (72-h) assay value. Relationships between mean and fasting glucose and mean glycemic assays were explored. Comparisons were also made between MPMG and glycemic assays. Finally, patients were divided into two groups according to magnitude of AUC-180, and relationships between MPMG, 1,5-AG, and mean A1C and FA were explored.

Data analysis

The statistical significance of differences was analyzed by the Student's *t* test. Correlation coefficients were determined using Pearson's correlation coefficients. Statistical significance was determined at $P < 0.05$. Calculation of means, SDs, correlations, and multivariate analyses were performed using WinSTAT for Excel (Fitch Software). AUC-180, MPMG, and mean overall glucose were measured with CGMS software. Comparisons of correla-

Table 2—Correlation between CGMS measures and glycemic assays

	Mean A1C	Mean 1,5-AG	Mean FA
Mean glucose			
<i>r</i>	0.27	-0.15	0.40
<i>P</i>	0.26	0.23	0.04
AUC-180 overall (n=34)			
<i>r</i>	0.36	-0.48*	0.33
<i>P</i>	0.02	0.002	0.03
AUC-180 at end interval 1 (n = 34)			
<i>r</i>	0.23	-0.36†	0.16
<i>P</i>	0.09	0.02	0.18
AUC-180 at end interval 2 (n = 33)			
<i>r</i>	0.35	-0.42*	0.37
<i>P</i>	0.02	0.008	0.02
Overall MPMG (n = 23)			
<i>r</i>	0.30	-0.50†	0.16
<i>P</i>	0.08	0.008	0.23

End interval for interval 1 is visit 2 (study midpoint) and for interval 2 is visit 3 (study end). Comparative correlations were calculated (27), and Steiger Z (1 bar) values were AUC-180 overall/A1C vs. AUC-180 overall/1,5-AG ($Z = -3.01$, $*P < 0.01$), AUC-180 interval 1/A1C vs. AUC-180 interval 1/1,5-AG ($Z = -1.99$, $†P < 0.05$), AUC-180 interval 2/A1C vs. AUC-180 interval 2/1,5-AG ($Z = -2.61$, $*P < 0.01$), MPMG/A1C vs. MPMG/1,5-AG ($Z = -2.24$, $†P < 0.05$).

tions were calculated using Steiger Z (1 bar) values (21).

RESULTS—Forty patients completed the study. Of these, six were excluded from the final analysis because of errors in a batch of samples that rendered the data unreliable due to concern that samples were mislabeled. Of the final 34 patients, there were 24 patients with type 1 diabetes, 10 patients with type 2 diabetes, 13 male subjects, and 21 female subjects (Table 1). We collected data at baseline, study midpoint, and study end (Table 1). The mean overall A1C was $7.29 \pm 0.56\%$. The mean overall 1,5-AG was $6.79 \pm 3.51 \mu\text{g/ml}$, and FA was $316 \pm 48.5 \mu\text{mol/l}$. Mean total AUC-180 ($13.5 \pm 7.6 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{day}^{-1}$) and overall MPMG values ($204 \pm 40 \text{ mg/dl}$) indicated that there was demonstrable postprandial hyperglycemia despite fair overall glycemic control, as demonstrated by A1C and mean CGMS glucose (mean $148 \pm 16 \text{ mg/dl}$).

Relationship between mean glucose and glycemic assays

We explored the relationship between glycemic assays (mean A1C, 1,5-AG, and FA) and average glycemic control, as determined by CGMS (Table 2). FA ($r = 0.40$, $P = 0.04$) and A1C ($r = 0.27$, $P = 0.26$) correlated better than 1,5-AG ($r = -0.15$, $P = 0.23$) to mean glucose as determined by CGMS, although only FA reached statistical significance.

Relationship between AUC-180 and glycemic assays

We then compared the relationship between AUC-180 (total or individual 72-h CGMS intervals) and glycemic assays (mean or end 72-h CGMS interval A1C, 1,5-AG, and FA). We found that mean 1,5-AG ($r = -0.48$, $P = 0.002$) correlated with total AUC-180 better than mean A1C ($r = 0.36$, $P = 0.02$) or FA ($r = 0.33$, $P = 0.03$) (Table 2). Likewise, study end 1,5-AG ($r = -0.49$, $P = 0.002$) cor-

related with total AUC-180 better than A1C ($r = 0.35$, $P = 0.02$) or FA ($r = 0.38$, $P = 0.01$). Comparisons between individual 72-h CGMS periods and either mean (Table 2) or end-interval glycemic assays (data not shown) did not change appreciably from total AUC-180. Other cutoffs for AUC (AUC-140, -160, and -200) showed similar correlation (data not shown). The correlation between 1,5-AG/AUC-180 was significantly greater than that of A1C/AUC-180 (Table 2). The partial correlation of 1,5-AG with AUC-180 (controlling for A1C) was -0.38 ($P = 0.01$), indicating that the relationship persisted for any given level of A1C.

Relationship between postmeal markers and glycemic assays

We also examined relationships between overall MPMG and glycemic assays in a subset of patients who entered meal markers into the CGMS device. We found that 1,5-AG ($r = -0.50$, $P = 0.008$) correlated better with overall MPMG than A1C ($r = 0.30$, $P = 0.08$) or FA ($r = 0.16$, $P = 0.23$) (Table 2). AUC-180 correlated highly with MPMG ($r = 0.77$, $P = 0.001$).

1,5-AG assay as an adjunct to A1C for postprandial hyperglycemia

To further investigate the clinical potential of these findings, patients were sorted by AUC-180 values and subdivided into two populations: bottom 50th percentile AUC-180 (17 patients) and top 50th percentile (17 patients). Table 3 presents A1C, 1,5-AG, FA, MPMG, and fasting glucose. Although A1C, FA, and fasting glucose are very similar, 1,5-AG and MPMG are significantly different between the bottom and top 50th percentiles.

As an example, we present data from two representative patients from each group. Patient 1 has a similar A1C (7.43%) to patient 2 (7.27%). In contrast, the 1,5-AG for patient 1 is within the normal range at $12.37 \mu\text{g/ml}$ vs. patient 2 at

Table 3—1,5-AG as an adjunct to A1C for postprandial hyperglycemia

	Total AUC-180 ($\text{mg} \cdot \text{dl}^{-1} \cdot \text{day}^{-1}$)	MPMG (mg/dl)	A1C (%)	1,5-AG ($\mu\text{g/ml}$)	FA ($\mu\text{mol/l}$)	Fasting glucose (mg/dl)
Bottom 50th percentile AUC-180	7.18 ± 4.45	180 ± 28 (n=12)	7.20 ± 0.71	8.00 ± 4.26	313 ± 55	146 ± 42
Top 50th percentile AUC-180	19.76 ± 3.88	230 ± 36 (n=11)	7.38 ± 0.35	5.58 ± 2.04	319 ± 43	158 ± 33
<i>P</i> value	<0.0001	0.001	0.34	0.04	0.70	0.36

Data are means \pm SD unless otherwise indicated.

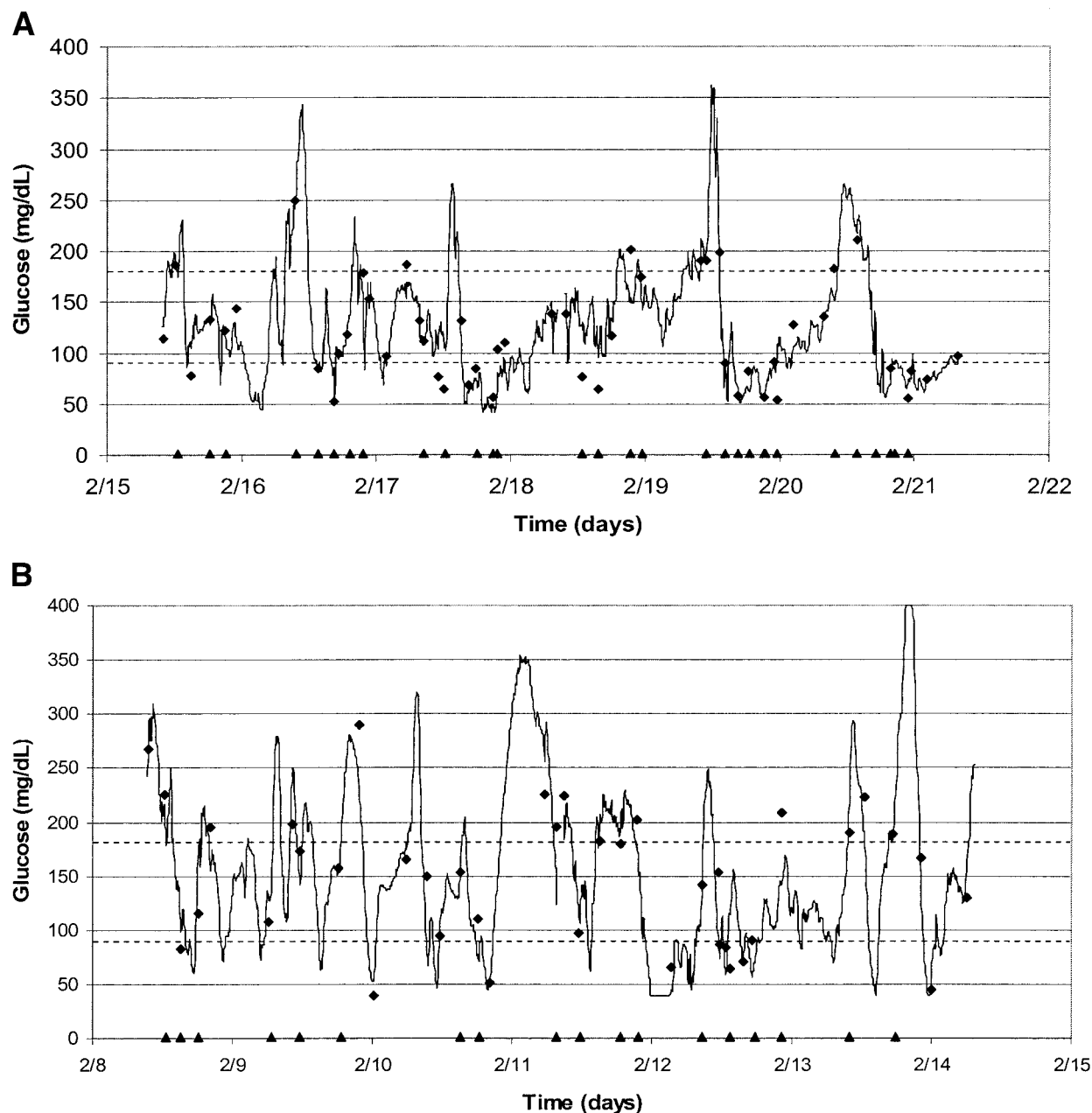


Figure 1—A: Patient 1: 52-year-old woman with type 1 diabetes, A1C 7.43%, 1,5-AG 12.37 $\mu\text{g/ml}$, AUC-180 $8 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{day}^{-1}$, and MPMG 195 mg/dl . B: Patient 2: 49-year-old man with type 2 diabetes, A1C 7.27%, 1,5-AG 4.5 $\mu\text{g/ml}$, AUC-180 $22 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{day}^{-1}$, and MPMG 235 mg/dl . \blacklozenge , paired meter glucose readings; \blacktriangle , meal markers; dashed lines, American Diabetes Association–recommended range of 90–180 mg/dl .

4.5 $\mu\text{g/ml}$. This also corresponds to a lower AUC (8 vs. $22 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{day}^{-1}$) and a lower MPMG (195 vs. 235 mg/dl) in patient 1 vs. patient 2, respectively. The CGMS tracings are shown for each patient and clearly demonstrate much greater glucose excursions in the patient with abnormal 1,5-AG (Fig. 1).

CONCLUSIONS— In a previous clinical study conducted in Japan, it was shown that 1,5-AG could be a useful index of glucose excursions in patients with

reasonably well-controlled diabetes (mean A1C 7.1%) (15). Preliminary data from another study in Japan showed that 1,5-AG was an independent predictor of postprandial hyperglycemia and was more sensitive and specific than A1C (22). Furthermore, a recent study showed that patients with type 2 diabetes receiving twice-daily biphasic insulin aspart 70/30 had significantly higher 1,5-AG levels than patients treated with glargine alone (23). Interestingly, many A1C levels below the target value of 7% in both treat-

ment populations were associated with low 1,5-AG levels. This suggests that excessive glycemic excursions were occurring in these subjects and perhaps that hypoglycemia contributed to overall lower A1Cs.

In this study, we compared glycemic test values to AUC-180, as measured by CGMS, and it was shown that the 1,5-AG assay reflects glycemic excursions more robustly than other established glycemic assays. This relationship persisted whether total AUC-180 over the entire

7-day period or individual 72-h AUC-180 was compared, indicating that variations in glucose excursions during shorter time intervals did not detract substantially from the overall association of 1,5-AG with glucose excursions. Also, whether mean or end-interval A1C, 1,5-AG, or FA was used, the relationship with AUC-180 persisted, suggesting that short-term variation in these analytes do not obscure the utility of these assays. This is important because 1,5-AG has been shown to exhibit significant changes (as early as 3 days) in response to rapid normalization of marked hyperglycemia (12,14). Thus, 1,5-AG might be useful in making changes to treatment regimens because of its ability to reflect consistent patterns of glucose excursions, not just isolated events.

The strength of the relationship between A1C and mean glucose was weak and may be explained by small sample size, particularly in light of the narrow range of A1Cs chosen for entry criteria and the relatively short duration of monitoring.

AUC-180 would be expected to reflect postprandial excursions in well-controlled patients and both postprandial and preprandial elevations in patients with poor control. When this relationship was explored, we found a strong correlation between AUC-180 and overall MPMG in this group of moderately controlled patients. AUC-180 was chosen as the primary measure of postprandial hyperglycemia due to its ease of measurement and because it would capture the true amount of time spent above a glucose value of 180 mg/dl, the average threshold for glucosuria, and the threshold above which 1,5-AG would be expected to drop. This was demonstrated by the tighter correlation of AUC-180 with urinary glucose compared with postmeal maximum values (data not shown). It is acknowledged that AUC-180 is an imperfect marker for postprandial hyperglycemia, as glucose excursions are not always meal related (24). In a subset of patients who entered meal markers into the CGMS, MPMG and AUC-180 correlated with 1,5-AG. However, both A1C and FA lost statistical significance. This may be due in part to the small sample size, but it underscores the importance of 1,5-AG as a marker for postprandial hyperglycemia. The unique relationship between 1,5-AG and postprandial glucose can only be applied to patients with moderate glycemic control at this point, because more marked hy-

perglycemia may reflect both fasting and postprandial glucoses in the 1,5-AG assay.

Our comparison of two patients' CGMS tracings further illustrates this point. Patient 1 clearly displays much fewer glycemic excursions than patient 2, despite similarities in A1Cs. In this population, 1,5-AG was a more sensitive indicator of glucose excursions than A1C, FA, or fasting glucose. This is reflected by 1,5-AG, which is much lower in patient 2. There also appears to be more periods of hypoglycemia in patient 2, and this is not reflected by the A1C.

Another key finding in this study was the marked variability in postmeal glucose levels in this subset of relatively stable, moderately controlled patients. Most notably, 1,5-AG was reflective of varying postmeal glucose levels, despite similarities in A1Cs. Thus, the 1,5-AG assay may facilitate achieving good glycemic control in patients with suboptimal A1Cs by identifying patients in whom postprandial glucose elevations predominate (25).

Due to the rapid response of 1,5-AG to changes in glycemia, serial 1,5-AG measurements may be useful in assessing postprandial hyperglycemia. This may be particularly valuable in examining the effect of therapy specifically targeted to postprandial glucose control. In most patients, it may be difficult to discern whether the true barrier to perfect glycemic control lies with inadequate prandial or basal glycemic treatment. There is often insufficient self-monitoring data to make the intricate adjustments that may be necessary in patients with type 1 diabetes on intensive insulin therapy. On the other hand, many patients with type 2 diabetes who are on oral agents check their blood glucoses only once or fewer times per day, generally in the fasting state. 1,5-AG may be useful as an adjunct to A1C in these settings.

In clinical practice, A1C and 1,5-AG may be used sequentially, first utilizing the A1C assay to identify patients who are moderately or well controlled (A1C 6.5–8.0%) and then using the 1,5-AG assay to determine the extent of postprandial glucose excursions. If the A1C is above target and the 1,5-AG is normal, therapy targeting basal glucose may be more useful. On the other hand, if the A1C is above target and the 1,5-AG is low, targeting postprandial glucose elevations may be more productive. This may involve more intensive postprandial monitoring or the addition of agents that specifically address

postprandial hyperglycemia. This hypothesis needs to be tested further in clinical trials. Future studies with larger sample sizes may show differences between subpopulations, such as type 1 versus type 2 diabetes (there were no significant differences in these groups in this study). It should be noted that 1,5-AG measurement may be less useful in the setting of intrinsic renal disease (26) and in pregnancy (27), where the renal threshold for glucose is altered.

1,5-AG reflects glycemic excursions, often in the postprandial state, more robustly than FA or A1C. 1,5-AG may be useful in conjunction with A1C to assess glycemic control in patients with moderate or good control.

Acknowledgments— This study was funded by Tomen America.

We express appreciation to the University of Rochester General Clinical Research Center and Michael McDermott, PhD, for his assistance on statistical calculations.

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