Assessment of the variance of the Ambulatory Glucose Profile over 3 to 20 days of continuous glucose monitoring

Timothy C. Dunn, PhD, Nathan Crouther, BS

Abbott Diabetes Care, Alameda, California

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Abstract

The Ambulatory Glucose Profile (AGP) has been proposed as an effective way to identify trends in glucose abnormalities in people with diabetes using continuous glucose monitoring (CGM)[1,2]. The aim of this study was to evaluate the minimum number of days of CGM needed to arrive at stable glucose patterns revealed by AGP analysis.

AGP analysis was performed utilizing 67 adult subjects (T1DM = 47, T2DM = 20) who participated in a study that began with 20 days of masked CGM, using the FreeStyle Navigator® System. Subjects were not able to see their CGM glucose values or trends and did not have glucose threshold or projected alarms available. Only masked data were evaluated in order to minimize effects of therapy adjustments on the evaluation. Statistics for each of 3 to 19 days of CGM data were compared to the 20-day values and evaluated on a per-subject basis. For overall summary statistics (mean, standard deviation, 10th, 25th, 50th, 75th, 90th percentiles, inter-quartile range, mean change in the hourly median curve), equivalence criteria of 90-110% of the 20-day value were evaluated. For overall percentages of glucose above, below or within the target of 3.89-7.78 mmol/L (70-140 mg/dL), the absolute difference compared to the 20-day value was evaluated at equivalence criteria (based on scaling the standard error of the overall mean) of 6.40%, 1.45%, and 5.46%, respectively. For hourly AGP percentile lines (10th, 25th, 50th, 75th, 90th) the mean absolute relative difference compared to the corresponding 20-day line was calculated and evaluated against the equivalence criteria <10%.

A summary of the 20-day statistics and the relationship between the number of days needed for an AGP statistic to meet the equivalence criteria for 70%, 80% and 90% of subjects is shown in **Table 2**. After 10 days, the glucose mean, standard deviation, 50th, 75th, and 90th percentiles are within 10% of the 20-day value for more than 80% of subjects. After 14 days, the percentages of above, below and within target, the 10th and 25th percentiles, and the hourly AGP percentile lines met the equivalence criteria for over 80% of patients. The interquartile range and mean change in the hourly median curve needed more days of CGM to approximate the 20-day value for 80% of subjects: 15 and 18 days, respectively.

AGP analysis promises to be an effective tool for identifying glucose abnormalities and may allow the use of evidence-based and protocol-driven medical practices to select appropriate therapies to address those abnormalities. Clinical evidence is lacking to support the assumption used in this study that AGP analysis of 20 days of CGM can identify clinically important glucose trends and patterns. Within that context, however, this analysis suggests that a minimum of 14 days of CGM provides identification of individual glucose patterns. Prospective studies are needed to provide clinical evidence establishing the benefits of identifying patterns with AGP analysis that affect treatment and improve outcomes.

FreeStyle Navigator® System

The FreeStyle Navigator® Continuous Glucose Monitoring System measures interstitial fluid glucose using a patient-inserted electrochemical sensor every minute, and records measurements for download every 10 minutes.

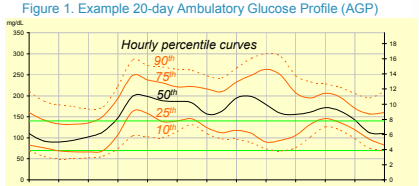
Aims

Assessment of multi-day continuous glucose monitoring trends and patterns is an important component of successful diabetes management.[3] Ambulatory Glucose Profile (AGP) analysis promises to become a widely-adopted and effective method for evaluating glycemic abnormalities and supporting treatment decisions to address abnormalities. The aim of this study was to investigate how AGP statistics vary by the number of days of continuous glucose monitoring available for analysis.

Methods

Masked continuous glucose monitoring (CGM) was performed for 20 days during a study of 123 participants in which real-time glucose values, trends, and alarms were not available. Therefore, it is likely that treatment changes during the masked CGM period were limited or did not occur.

Figure 1. Example 20-day Ambulatory Glucose Profile (AGP)



Ambulatory Glucose Profile (AGP) analysis considers glucose values as if they were collected in a single 24-hour period and provides summaries of the CGM glucose values overall and by five curves that indicate the distribution of glucose values by hour of the day (**Figure 1**).

67 of 123 participants were analyzed (**Table 1**) that had at least 19 of the 20 days with at least one CGM measurement in each of 12 hours of the day. Statistics for each of 3 to 19 days of CGM were compared to the 20-day statistics and evaluated on a per-subject basis. Criteria for "clinical equivalence" were selected for each statistic (**Table 2**):

- within three standard errors of the population mean of the participant's 20-day value for percentage within, above, and below target (3.89 - 7.78 mmol/L, 70 - 140 mg/dL)
- within 10% mean absolute relative difference (MARD) for the hourly percentile curves
- absolute relative difference (ARD) of less than 10% for the remaining statistics: mean, standard deviation, 10th, 25th, 50th, 75th, 90th percentiles, inter-quartile range, mean change in median curve.

The number of days of CGM needed to be considered similar to the 20-days of CGM was selected if at least 80% of the participants met the equivalence criteria.

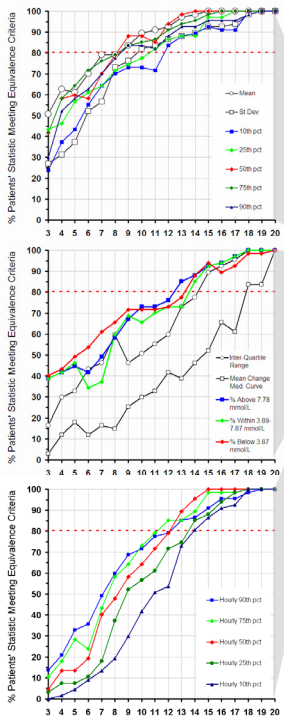
Table 1. Participant Characteristics

Demographics		Frequency / N (%)
Gender	Female	42 / 67 (62.7 %)
	Male	25 / 67 (37.3 %)
Diabetes	Type 1	47 / 67 (70.1 %)
	Type 2	20 / 67 (29.9 %)
Ethnicity	Caucasian	49 / 67 (73.1 %)
	Non-Caucasian	18 / 67 (26.9 %)
Age	18-34	7 / 67 (10.4 %)
	35-54	39 / 67 (58.2 %)
	55+	21 / 67 (31.3 %)

Characteristics	N	Mean ± SD (Min, Max)
Age (years)	67	50.0 ± 11.5 (19.5, 72.6)
Body Mass Index (BMI, kg/m²)	67	28.5 ± 5.6 (18.9, 41.6)
Duration of Diabetes (years)	67	23.1 ± 11.7 (3.6, 48.5)
Daily total insulin dosage (units)	67	49.6 ± 28.1 (12, 126)

Results

Figure 2. 20-day AGP statistics and number of CGM days needed to reach equivalence



For more than 80% of participants (**Table 2**):

- After 10 days of CGM, the glucose mean, standard deviation, 50th, 75th, and 90th percentiles were within 10% of the 20-day values
- After 14 days of CGM, the rates of above, below and within target, the 10th and 25th percentiles, and the hourly AGP percentile lines met 20-day equivalence criteria
- The interquartile range and mean change in the hourly median curve met 20-day equivalence criteria after 15 and 18 days, respectively

Table 2. Summary of 20-day AGP statistics and number of CGM days needed to reach equivalence

Ambulatory Glucose Profile Statistic	Mean (SD) [Min, Max] of 20-day Values for Participants	Criteria for Equivalence with 20-day Statistic	Number of Days to Meet Equivalence Criteria (% of Participants) 70%	80%	90%
Mean	9.6 (1.8) [6.3, 13.6] mmol/L	ARD < 10%	6	9	11
Standard Deviation	3.4 (0.8) [1.9, 5.4] mmol/L	ARD < 10%	8	10	15
10th percentile	5.7 (1.3) [3.4, 8.5] mmol/L	ARD < 10%	8	12	15
25th percentile	7.3 (1.6) [4.6, 10.8] mmol/L	ARD < 10%	8	11	15
50th percentile	9.4 (1.8) [6.1, 13.5] mmol/L	ARD < 10%	7	9	12
75th percentile	11.7 (2.2) [7.3, 17] mmol/L	ARD < 10%	6	9	12
90th percentile	13.9 (2.5) [8.7, 21.2] mmol/L	ARD < 10%	7	9	13
Inter-Quartile Range	4.4 (1.2) [2.2, 7.7] mmol/L	ARD < 10%	13	15	16
Mean Change in Median Curve	0.6 (0.2) [0.2, 1.2] (mmol/L)/h	ARD < 10%	18	18	-
% Above 7.78 mmol/L	63 (18.1) [19, 92] %	AD < 6.40%	10	13	15
% Within 3.89 - 7.78 mmol/L	33 (15.4) [8, 74] %	AD < 5.46%	11	14	15
% Below 3.87 mmol/L	4.2 (4.1) [0, 15.8] %	AD < 1.45%	9	14	15
Hourly 10th Percentile Curve	-	MARD < 10%	13	14	16
Hourly 25th Percentile Curve	-	MARD < 10%	12	14	16
Hourly 50th Percentile Curve	-	MARD < 10%	11	13	14
Hourly 75th Percentile Curve	-	MARD < 10%	10	12	15
Hourly 90th Percentile Curve	-	MARD < 10%	10	13	15

ARD = Absolute Relative Difference
AD = Absolute Difference
MARD = Mean Absolute Relative Difference

Figure 3. Example patient of 3, 7 and 14-day AGPs compared to the 20-day AGP (shaded area)

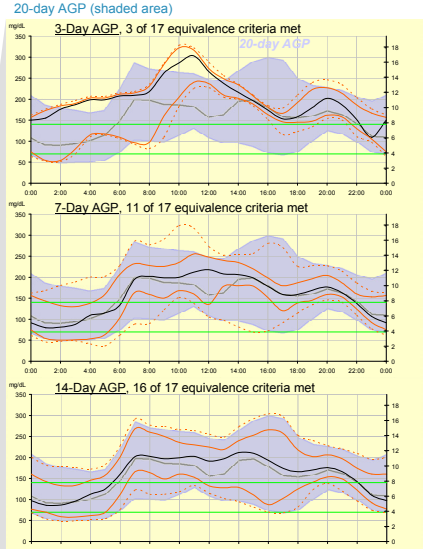


Table 3. Example patient of 3, 7, 14, and 20-day AGP statistics

Ambulatory Glucose Profile Statistic	3-day	7-day	14-day	20-day
Mean (mmol/L)	9.8	8.6	9.0	8.7
Standard Deviation (mmol/L)	3.5	3.7	4.0	3.8
10th percentile (mmol/L)	7.2	5.0	5.0	4.8
25th percentile (mmol/L)	7.9	7.0	6.4	6.2
50th percentile (mmol/L)	11.1	8.8	9.0	8.5
75th percentile (mmol/L)	12.1	10.8	11.4	11.0
90th percentile (mmol/L)	12.5	13.1	13.2	13.0
Inter-Quartile Range (mmol/L)	4.2	3.8	5.0	4.8
Mean Change in Median Curve (mmol/L)/h	1.1	0.7	0.7	0.8
% Above 7.78 mmol/L	73.6%	60.5%	61.0%	55.1%
% Within 3.89 - 7.78 mmol/L	21.2%	27.4%	29.1%	36.4%
% Below 3.87 mmol/L	5.2%	12.1%	9.9%	8.5%
Hourly 10th Percentile Curve (MARD)	31.0%	16.7%	4.9%	0%
Hourly 25th Percentile Curve (MARD)	30.6%	18.1%	7.1%	0%
Hourly 50th Percentile Curve (MARD)	22.5%	7.3%	6.6%	0%
Hourly 75th Percentile Curve (MARD)	18.7%	7.8%	3.3%	0%
Hourly 90th Percentile Curve (MARD)	17.7%	9.0%	1.9%	0%

Red = Statistic met 20-day equivalency criteria
MARD = Mean Absolute Relative Difference

Conclusions

This analysis suggests that while some patients have consistent glycemic trends and patterns within each 24-hour period, many do not. If intermittent use of CGM is being contemplated clinically, it is important to understand the trade-offs of collecting more days of CGM -- incurring additional expense and potential patient inconvenience -- versus insufficient days of CGM that may mislead or mis-identify clinically important glycemic patterns. It is unlikely that any *a priori* criteria will distinguish patients with consistent glycemic trends and patterns. Therefore, this analysis guides selection of the number of days required to feel confident in the trends and patterns revealed by CGM in a majority of patients.

This study is exploratory in nature, and has several limitations. First, the analysis retrospectively analyzed a subset of data available from a study conducted with alternate primary aims.[4] The subset was selected based on a high level of successful masked CGM over a 20-day period. Therefore, participants were removed who had technique or technical problems that may occur more in a realistic, broader population outside of a clinical trial. Second, the results are highly dependent on the selection of criteria for statistical equivalence. Since there is a lack of evidence for establishing those criteria, the criteria were selected based on judgment of the authors. Alternate criteria may have dramatic influence on the results. For example, additional analyses indicated, that a stricter ARD criteria of less than 5% for mean glucose increased by 4 days (to 13 days) the number needed for 80% of participants to meet the 20-day equivalence criteria, while a more relaxed ARD criteria of less than 15% decreased the number of days needed by 4 (to 5 days).

With those limitations in mind, the analysis recommends that 14 days of CGM reveals consistent glycemic patterns in a majority of patients that would be revealed after 20 days of CGM. In other words, to get a clinically relevant "glycemic snapshot" for a patient, two weeks of CGM may be a justified healthcare resource investment. However a third week over and above the initial two weeks may have limited benefit for improving the assessment of glycemic patterns and trends.

The analysis also indicates that less than 7 days of CGM may be insufficient to correctly identify clinically important glycemic trends and patterns, as the summary metrics and trends and patterns revealed by AGP analysis are not close to those that would be revealed after additional days of CGM for a large majority of patients.

Future prospective intervention studies are needed to generate evidence of the clinical utility of intermittent CGM. Furthermore, those studies could establish the sensitivity of interventions to the precision of glucose summary statistics, for example those provided by AGP analysis.

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