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

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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). The aim of this study was to evaluate the minimum number of days of CGM needed to arrive at reliable diagnostic and treatment decisions 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 access to any other blood glucose information. Only masked data were evaluated in order to minimize effects of therapy adjustments on the evaluation. For statistical analysis, each subject’s data were divided into 3 to 19 days of CGM data were compared to the 20-day value and evaluated on a per-subject basis. For overall summary statistics (mean, standard deviation, 50th, 25th, 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 the standard error of the mean) of 6.4%, 14.4%, and 5.4%, respectively. For hourly AGP percentile lines (10th, 25th, 50th, 75th, 90th) the mean absolute relative difference (MARD) compared to the corresponding 20-day line was calculated and evaluated against the equivalence criteria of 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, 25th and 90th percentiles were for more than 80% of subjects. After 14 days, the percentages of above, below and within target, the 10th and 25th, and the hourly AGP percentile lines met the equivalence criteria for over 80% of patients. The inter-quartile range and mean change in the hourly median curve needed more days of CGM to approximate the 20-day value for 80% of subjects.

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 validate clinical evidence establishing the benefits of identifying patterns with AGP analysis that affect treatment and improve outcomes.

Aims
Assessment of multi-day continuous glucose monitoring trends and patterns is an important component of successful diabetes management. Ambulatory Glucose Profile (AGP) analysis promises to become a widely adopted and effective method for evaluating glucose 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.

Results
Ambulatory Glucose Profile (AGP) analysis considers glucose trends as if they were collected in a single 24-hour period and provides summaries of the CGM glucose values overall and by five 4-hour time blocks. This figure indicates the distribution of glucose values by hour of the day (Figure 1).

Ambulatory Glucose Profile (AGP) analysis considers glucose trends as if they were collected in a single 24-hour period and provides summaries of the CGM glucose values overall and by five 4-hour time blocks. 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 participants. The analysis suggests that 14 days of CGM may be insufficient to correctly identify clinically important glycemic trends and patterns, and 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.

Conclusions
This study is exploratory in nature, and has several limitations. First, the analyses were applied to the subset of data available from a study conducted with alternative primary aim. The subset was selected based on a high level of successful masked CGM over a 20-day period. Therefore, participants were removed who had technical or technical problems that may occur in a realistic, broader population outside of a clinical trial. Second, the analysis 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 AHR criteria of within 10% mean absolute relative difference 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 AHR criteria of less than 15% decreased the number of days needed by 4 to 5 days.

With these 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 justified as a healthcare decision. However, a third week over and above the initial two weeks may have limited benefit for improving the assessment of glycemic trends and patterns.

The analysis suggests that less than 7 days of CGM may be insufficient to correctly identify clinically important glycemic trends and patterns, and 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 use. It is possible that 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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References

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

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

FreeStyle Navigator System

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

Acknowledgments

This analysis suggests that while some patients have consistent glycemic trends and patterns within each 24-hour period, many do not. Interpreting 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 mask or mis-identify clinically important glycemic patterns. It is unlikely that any a priori criteria will distinguish patients with consistent glycemic patterns. Therefore, analysis of the number of days of CGM needed 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 different primary aim. The subset was selected on the basis of a high level of successful masked CGM over a 20-day period. Therefore, participants were removed who had technical or technical problems that may occur in a realistic, broader population outside of a clinical trial. Second, the analysis 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 AHR criteria of 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 AHR criteria of less than 15% decreased the number of days needed by 4 to 5 days.

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