Investigation of the Minimum Duration Needed to Estimate the Percentile Values for Target Duration in Ambulatory Glucose Profile

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Background

- Ambulatory glucose profile (AGP) is effective in grasping glycemic variability and determining therapeutic strategy [1, 2].
- In AGP for intermittently scanned continuous glucose monitoring (isCGM), it is common for patients to intervene at the time when the interquartile range of glucose levels deviates from the target range [1, 2].
- It is important to consider the cases having glucose levels with missing values measured using isCGM.
- There are limited investigations regarding the “minimum duration needed to estimate percentile values of glucose levels for target duration” (MDpercentile).

1. Kröger, et al. J Diabetes Sci Technol. 2020; 14: 586–594.
2. Czupryniak L, et al. Diabetes Ther. 2022; 13: 811–821.

Research design & Methods

- This is a cross-sectional study.
- In Analysis 1, we analyzed the glucose levels without missing values measured using CGM (FreeStyle Libre Pro) over 24 h for 13 days (from 00:00 on Day 2 to 00:00 on Day 15; CGM attachment: Day 1) for 100 outpatients with type 2 diabetes, who did not change their diabetic treatment through the CGM-wearing duration.
- In Analysis 2, we analyzed the glucose levels with missing values measured using isCGM (FreeStyle Libre) over 24 h for 60 days (from 00:00 on Day 31 to 00:00 on Day 91; isCGM attachment: Day 1) for 50 outpatients with type 2 diabetes, who did not change their diabetic treatment through the isCGM-wearing duration.
- In Analysis 1, MDpercentile for the 2-h mean glucose level for 13 days (MDpercentile2h13days) was provided by correlation coefficient analysis using R^2=0.9 as the threshold [3–5].
- In Analysis 2, MDpercentile for the 24-h mean glucose level for 60 days (MDpercentile24h60days) was provided by correlation coefficient analysis using R^2=0.9 as the threshold [3–5].

- Primary endpoints
  Average of MD2h13days in Analysis 1 and MD24h60days in Analysis 2
- Secondary endpoints
  MD2h13days in Analysis 1
  “Histogram showing the distribution of all sensor glucose levels of Libre Pro on day 8 in 100 patients (n=9600: no blank)” (histogram for Libre Pro).
  “Histogram showing the distribution of all sensor glucose levels of Libre on day 90 in 50 patients (n<4800: with blank)” (histogram for Libre).
- Simulation endpoints
  Simulated glucose levels (SiGL) created to assess the influence of glucose levels’ distribution in population on percentile values in the population

Results and Discussion

Characteristic	Analysis 1	Analysis 2
N (Male / Female)	100 (60 / 40)	50 (30 / 20)
Age, years	69.5 ± 13.4	66.2 ± 12.8
BMI, kg/m^2	24.2 ± 4.1	24.7 ± 5.6
HbA1c, %	8.0 ± 1.5	8.5 ± 2.0
5% of 24-h MGL for TD	119.8 ± 35.1	100.4 ± 22.4
25% of 24-h MGL for TD	142.2 ± 41.9	128.5 ± 27.8
50% of 24-h MGL for TD	163.9 ± 47.5	152.2 ± 32.9
75% of 24-h MGL for TD	189.4 ± 55.8	179.6 ± 39.7
95% of 24-h MGL for TD	223.4 ± 64.3	224.4 ± 54.7

Table 1: Baseline characteristics
Data are shown as mean ± standard deviation.
BMI, body mass index; HbA1c, hemoglobin A1c, 5% of 24-h MGL for TD, 5 percentile value of 24-h mean glucose level for target duration

Libre Pro	MDpercentile2h13days, day												
	0AM-2AM	2AM-4AM	4AM-6AM	6AM-8AM	8AM-10AM	10AM-12AM	0PM-2PM	2PM-4PM	4PM-6PM	6PM-8PM	8PM-10PM	10PM-12PM	Average
5%	7	6	8	7	8	7	8	8	8	7	7	7	7.42
25%	6	8	8	10	7	8	8	7	6	5	7	7	7.25
50%	8	8	7	5	6	7	8	7	7	6	8	6	6.92
75%	7	7	7	6	6	7	7	7	7	8	7	7	6.92
95%	6	6	6	5	6	7	6	6	5	6	6	6	5.92
Average	6.8	7	7.2	6.6	6.6	7.2	7.4	7	6.6	6.6	7	6.6	

Table 2: MD2h13days in Analysis 1
MD2h13days were analyzed using Pearson's product-moment correlation coefficient
MD2h13days, minimum duration needed to estimate percentile values of 2-h mean glucose level for 13 days; 5%, MD2h13days for 5 percentile value

Libre	MDpercentile24h60 days, day (60 days)
	24-h
5%	26
25%	17
50%	15
75%	13
95%	45
Average	23.2
Measuring rate, %	91.5

Table 3: MD24h60days in Analysis 2
MD24h60days were analyzed using Pearson's product-moment correlation coefficient
MD24h60days, minimum duration needed to estimate percentile values of 24-h mean glucose level for 60 days; 5%, MD24h60days for 5 percentile value; Measuring rate, number of sensor glucose levels measured for 60 days ÷ 96 ÷ 60 × 100 (%)

- In Analysis 1, the lower percentile values needed more days to predict the percentile values.

The results of MD2h13days suggest that more days are needed to predict the percentile values during nighttime and before and after lunch.
Increased day-to-day variability during nighttime may be due to hypoglycemia existed intermittently at the same time zone daily.
Patients may have sometimes had less or no breakfast.
Patients may have sometimes had lunch including much carbohydrate rapidly.

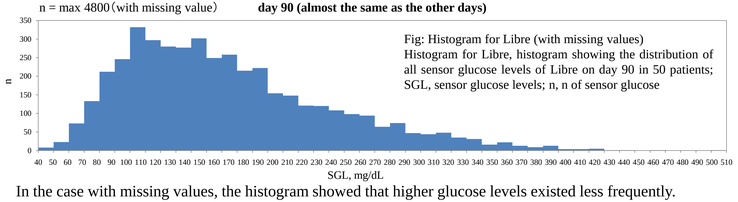

Fig: Histogram for Libre (with missing values)
Histogram for Libre, histogram showing the distribution of all sensor glucose levels of Libre on day 90 in 50 patients; SGL, sensor glucose levels; n, n of sensor glucose

In the case with missing values, the histogram showed that higher glucose levels existed less frequently.
In this case, missing higher glucose levels leads to large change of the higher percentile values. This is because the change of population and relative ranks largely change the higher percentile values due to decreased existence frequency of glucose levels.

	SiGL 1, mg/dL	SiGL 2, mg/dL	SiGL 3, mg/dL
	100	100	
	101	101	101
	102	102	102
	104	104	104
	108	108	108
	116	116	116
	132	132	132
	164	164	164
	228	228	228
	356		356
5%	100.5	100.4	101.4
25%	102.5	102	104
50%	112	108	116
75%	156	132	164
95%	298.4	202.4	304.8

Table 4: Simulated glucose levels created to assess the influence of glucose levels’ distribution in population on percentile values in the population
SiGL, simulated glucose levels; 5%, 5 percentile values in the population

The SiGL in table 4 were created with the concept that the fact that, “higher glucose levels exist less frequently”, is equal to the fact that, “interval between higher glucose levels are wider when glucose levels exist equally”, in that median values are biased to hypoglycemia side. The results in SiGL 1 and 2 suggest that absence of the maximum value causes extreme decrease in the 95-percentile value (298.4 mg/dL→202.4 mg/dL). The results in SiGL 1 and 3 suggest that absence of the minimum value does not almost affect the 5-percentile value (100.5 mg/dL→101.4 mg/dL).

Large change of the higher percentile values leads to change of ranks within the population, resulting in lower correlation coefficients. From the above, when there are missing data, higher percentile may be associated with longer MD due to lower correlation coefficients. Therefore, when the higher percentile values are used to determine intervention, the degree of missing should be grasped to examine the credibility.

3. Riddlesworth TD, et al. Diabetes Technol Ther. 2018; 20:314-6.
4. Xing D, et al. Diabetes Technol Ther. 2011; 13:351-8.
5. Camerlingo N, et al. American Diabetes Association’s 80th Scientific Sessions. 2020; poster presentation:877-P.

- In Analysis 2, the 95-percentile value needed the most days to predict the percentile value.

Randomness of the amount of breakfast may have randomized the timing of increase of glucose levels and endogenous insulin secretion due to first meal, resulting in increased day-to-day variability before and after lunch.
In addition, having lunch including much carbohydrate rapidly at random may have resulted in increased day-to-day variability before and after lunch.
If there are missing data during nighttime or before and after lunch, intervention should be determined carefully.

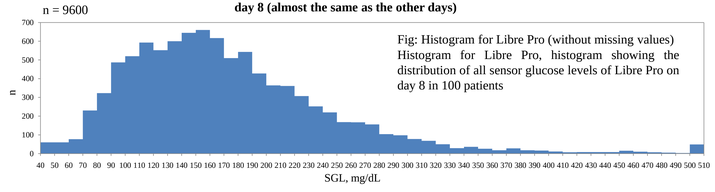

Fig: Histogram for Libre Pro (without missing values)
Histogram for Libre Pro, histogram showing the distribution of all sensor glucose levels of Libre Pro on day 8 in 100 patients

In the case without missing values, the histogram showed that higher glucose levels existed less frequently.
Higher glucose levels were associated with increased differences of glucose levels between patients due to decreased existence frequency of glucose levels, resulting in keeping the day-to-day correlation coefficients, namely, shorter MD.
This is statistical reasons, and this result does not show that higher glucose levels are easy to be predicted in clinical practice.
The reason why MD became longer, namely the day-to-day correlation coefficients decreased, although the glucose levels existed less frequently when the glucose levels were less than 100 mg/dL, may be because hypoglycemia may have existed intermittently over 13 days at the same time zone. The intermittently hypoglycemia may have raised day-to-day glycemic variability within the patients, in low glucose levels area.

- This study results are based on the histogram of glucose levels in patients with type 2 diabetes in community hospital, namely, based on the distribution that higher glucose levels exist less frequently.
- For example, if data including many patients with type 1 diabetes having high glycemic variability are analyzed, hyperglycemia and hypoglycemia seem to increase, resulting in flattening histogram. In this case, the results that higher percentile leads to shorter MD and higher percentile is susceptible to missing data may diminish.
- In clinical practice, predicting the distribution of glucose levels for patients and comparing to the theory should be done to determine intervention.

Conclusion

- Lower percentile values may need more days to predict the percentile values in the calculation using glucose levels without missing values.
- Quite high percentile values may need many days to predict the percentile value in the calculation using glucose levels with missing values.

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