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THE MINIMUM DURATION NEEDED TO ESTIMATE 24H TIME IN RANGE

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Background

- It is useful for patients using a personal CGM to know the minimum duration [MD] from 0:00 needed to estimate “time in range (70–180 mg/dL) [TIR] from 0:00 to 24:00” (24h–TIR), to know appropriate intervention time to achieve target 24h–TIR.

Research design & Methods

- In a cross-sectional study, we analyzed 24h glucose levels measured using CGM (iPro2) for 150 patients with type 2 diabetes.
- We calculated TIR, corresponding to 173 extracted durations (ED) [0:00–09:40, 0:00–09:45…0:00–24:00: 40–100% of 24h (40–100%)] (EDTIR).
- We arranged patients in descending order of 24h–TIR, ranking from 1 to 150. Then, 80 patients were selected 21 times as shown in Table 1.
- MD needed to estimate 24h–TIR were provided by correlation coefficient analysis using R^2=0.9 as threshold, in all patients and corresponding to the 21 groups.

Example

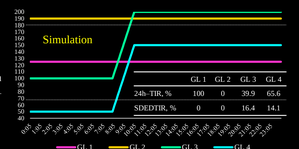
Rank	24h–TIR
1	100
2	99
3	98.6
.	
.	
148	3.5
149	1.7
150	0

Table 1

Group number	Selected groups
1	51–130
2	1–3, 54–129, 150
3	1–6, 57–128, 149–150
4	1–9, 60–127, 148–150
5	1–12, 63–126, 147–150
6	1–15, 66–125, 146–150
7	1–18, 69–124, 145–150
8	1–21, 72–123, 144–150
9	1–24, 75–122, 143–150
10	1–27, 78–121, 142–150
11	1–30, 81–120, 141–150
12	1–33, 84–119, 140–150
13	1–36, 87–118, 139–150
14	1–39, 90–117, 138–150
15	1–42, 93–116, 137–150
16	1–45, 96–115, 136–150
17	1–48, 99–114, 135–150
18	1–51, 102–113, 134–150
19	1–54, 105–112, 133–150
20	1–57, 108–111, 132–150
21	1–60, 131–150

➢ The aim of the select shown in Table 1

- We assumed that the number of patients increased as the patients’ 24h–TIR increased because study participants were patients with type 2 diabetes in community hospital (“Assume 1”).
- We also assumed theoretically that patients with 24h–TIR of around 50% had high SDEDTIR at least for the case where minimum EDTIR was 40% because, in the case where glucose levels were within 70–180 mg/dL during nighttime and those were out of 70–180 mg/dL during daytime, and vice versa, as shown in GL 3 and 4 in the simulation data, the 24h–TIR became around 50% with high SDEDTIR (“Assume 2”).
- We set the start of select as ranks 51–130, intending that the median of 24h–TIR were much grater than 50% due to “Assume 1” and intending “Assume 2”.



Endpoints

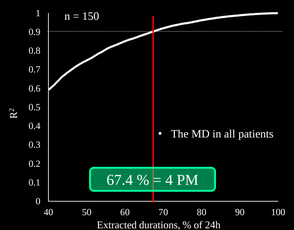
- The MD in all patients
- Correlation between 24h–TIR and standard deviation (SD) of 173 EDTIR [SDEDTIR]
- Distribution of 24h–TIR and SDEDTIR
- Correlation between mean of SDEDTIR (MSDEDTIR) and MD (n=21)

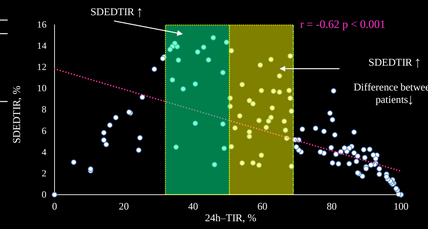
Result and Discussion

Patient characteristics

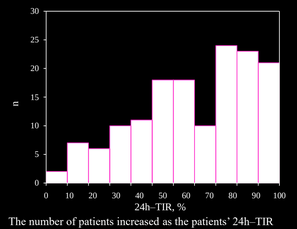
Characteristic	Values
N (Male / Female)	150 (86 / 64)
Age, years	69.3 ± 13.7
BMI, kg/m^2	24.6 ± 5.0
HbA1c (NGSP), %	9.0 ± 1.8
24h–TIR, %	69.1

Data are shown as mean ± SD.





- 24h–TIR correlated to standard deviation (SD) of 173 EDTIR [SDEDTIR].
- 24h–TIR for patients who had high SDEDTIR was mainly concentrated in the range (30%–70%), and patients whose 24h–TIR was in the range (0%–30%, 30%–100%) had low SDEDTIR.



- The number of patients increased as the patients’ 24h–TIR increased.
- Mean of SDEDTIR (MSDEDTIR) correlated to MD (r=0.998, p<0.001) (n=21).

r: Pearson’s product moment correlation coefficient

1. starting to select the patients in the colored area; 2. dividing the patients into 2 groups; 3. shifting the select to high and low 24h–TIR
The above process leads to lower frequent high SDEDTIR and higher frequent low SDEDTIR.

Higher 24h–TIR leads to lower differences in 24h–TIR between patients and lower SDEDTIR, resulting in offset for influence on MD.
Lower 24h–TIR leads to higher differences in 24h–TIR between patients and lower SDEDTIR, resulting in shorter MD.

Group number	MSDEDTIR (%)	MD (% of 24h)
1	7.1	85.8
2	6.8	82.6
3	6.6	80.2
4	6.3	78.5
5	6.1	75.3
6	5.8	73.6
7	5.5	71.5
8	5.3	69.4
9	5.0	68.4
10	4.8	66.7
11	4.6	65.6
12	4.3	63.2
13	4.1	60.1
14	3.8	57.3
15	3.6	55.9
16	3.5	52.4
17	3.4	52.8
18	3.2	50.3
19	3.2	51.7
20	3.0	50.0
21	3.1	50.3

Correlation coefficient analysis

➢ The data were analyzed using Pearson's product moment correlation coefficient. However, explanation using Spearman's rank correlation coefficient is easier to understand. Therefore, we explain using Spearman's rank correlation coefficient. The theory for Spearman's rank correlation coefficient is almost the same as the theory for Pearson's product moment correlation coefficient.

Spearman's rank correlation coefficient

$$r_s = 1 - \frac{6\sum_{i=1}^{n} d_i^2}{n(n^2-1)}$$

Simulation

A	B	Rank in A (RaA)	Rank in B (RaB)	(RaA - RaB)^2
1	1	1	1	0
2	2	2	2	0
3	3	3	3	0
4	4	4	4	0
5	5	5	5	0
6	6	6	6	0
7	7	7	7	0
8	8	8	8	0
9	9	9	9	0
				1 r

➢ In the left table, the rank of the number in group A and the rank of the number in group B perfectly correspond as shown. Like this, more correspondence of “ranks within the population” between relative pairs leads to stronger correlation.

A	B	RaA	RaB	(RaA - RaB)^2
1	4	1	4	9
2	7	2	7	25
3	2	3	2	1
4	9	4	9	25
5	5	5	5	0
6	1	6	1	25
7	8	7	8	1
8	3	8	3	25
9	6	9	6	9
				0 r

➢ In the right table, the rank in A and the rank in B do not correspond. Like this, change of “ranks within the population” leads to less correspondence between relative pairs, resulting in weaker correlation.

We explain about 2 important contents which are brought by the characteristics of correlation coefficient analysis.

	I	II	III	IV	V	VI	CV
A	100	101	99	101	99	100	0.89
B	90	89	91	89	91	90	0.99
C	80	81	79	81	79	80	1.12
D	70	69	71	69	71	70	1.28
E	60	61	59	61	59	60	1.49
F	50	49	51	49	51	50	1.79
G	40	41	39	41	39	40	2.24
H	30	29	31	29	31	30	2.98
I	20	21	19	21	19	20	4.47
J	10	9	11	9	11	10	8.94

	I	II	III	IV	V	VI	CV
A	10	11	9	11	9	10	8.9
B	9	8	10	8	10	9	9.9
C	8	9	7	9	7	8	11.2
D	7	6	8	6	8	7	12.8
E	6	7	5	7	5	6	14.9
F	5	4	6	4	6	5	17.9
G	4	5	3	5	3	4	22.4
H	3	2	4	2	4	3	29.8
I	2	3	1	3	1	2	44.7
J	1	0	2	0	2	1	89.4

We explain about 2 important contents which are brought by the characteristics of correlation coefficient analysis.

1, Increased relative variability within rows increases the possibility of decreased correlation coefficient due to change of ranks within columns. The coefficient of variation within rows is 10 times higher in the right table than that in the left table. In the left table, ranks within columns do not change as shown because variability within rows is relatively low, however, in the right table, ranks within columns change as shown because variability within rows is relatively high, namely 10 times compared to the left table. In this case, correlation coefficients between consecutive columns become lower in the right table than in the left table.

2, Decreased differences in mean within rows between rows increases the possibility of decreased correlation coefficient due to change of ranks within columns. In the left table, mean within rows varies by 10 mg/dL between consecutive rows, however, in the right table, that varies by only 1 mg/dL between consecutive rows. In the left table, ranks within columns do not change as shown because the differences of the mean between consecutive rows are high, however, in the right table, ranks within columns change as shown because the differences of the mean between consecutive rows are low. In this case, correlation coefficients between consecutive columns become lower in the right table than in the left table.

From the above, correlation coefficients between consecutive columns become lower with higher variation within rows and lower differences between consecutive rows.

Conclusion

➢ Patients should intervene to achieve target 24h–TIR by at least 16:00.

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Glycemic variability (GV)	CV of patients with mean GV	MD	Element
AOC<70	363.7	40.3	B
TBR<70	284.9	40.3	C
Hypoglycemic Index	258.4	40.3	B
LBGI	203.0	40.3	B
IGC	119.4	48.3	B
TBR<54	447.6	50.7	C
GVP	67.7	53.1	Q
MAG	39.1	54.9	Q
CONGA1	49.3	55.2	Q
Mean	24.3	62.5	Q
TAR>140	53.9	63.2	C
TIR70-140	63.4	64.9	C
AUC>140	96.3	65.6	B
HBGI	93.3	66.0	B
TAR>180	93.6	66.3	C
J-index	51.8	67.4	Q
TIR70-180	38.9	67.4	C
M value (100)	98.7	68.4	Q
ADRR	61.9	69.8	Q
AUC>180	136.4	70.1	B
CV	44.9	70.8	Q
CONGA2	49.5	72.2	Q
CONGA4	49.0	72.6	Q
SD	48.0	72.6	Q
CONGA3	48.8	73.3	Q
Median	25.5	74.0	Q
TAR>250	173.3	75.7	C
Hyperglycemic Index	74.1	76.0	B
Interdecile range	48.3	77.4	Q
Interquartile range	56.1	81.3	Q

➢ Element C: category element
Q: quantitative element B: having both elements

☆ We scored GV to visualize the effect of GV metric’s characteristic on MD, based on the above consideration. Higher score means stronger effect on shorter MD.

Score	GV	GV	GV	GV	GV	GV	GV	GV
Raise “CV of patient”	10	0	0	3	5	0	5	0
Reduce “CVEDGV”	3	5	10	4	3	5	0	3
Irreversible element	7	10	3	4	4	3	0	3
Averaging	5	5	5	5	2	5	5	0
Total	25	20	18	16	14	13	10	6

➢ Regarding score for averaging

GVs excepting ADRR, median, interdecile range, and interquartile range are sure to include averaging in calculation process. ADRR, median, interdecile range, and interquartile range got a score of 0, as the basis. GV colored in skin color include M value and ADRR. Because M value includes max and min GL in calculation process, we gave a score of 4. Therefore, total score of GV colored in skin color becomes 2. We gave a score of 5 to GVs excepting those colored in lavender and skin color.

➢ Regarding score for raising “CV of patient”

GV with Q element had a score of 0, as the basis. Regarding the other GV, we scored referring to the actual “CV of patient”. High CV element for GV colored in yellow was lower than the other GV with High CV element. Thus, the score of GV colored in yellow was subtracted.

➢ Regarding score for reducing “CVEDGV”

GVs colored in green and peony had a score of 5 as the normal so that a score of GV colored in red was max score of 10 and a score of GV colored in gold was min score of 0. GV colored in red, namely mean-related GV metrics, got max score of 10 because they have lower CVEDGV than the other GV with Q element. GV colored in gold got a score of 0 because they have the highest CVEDGV among all the metrics. The score of 3 above was determined as a middle of min and normal score. The score of 4 above was determined as a middle of the 3 and normal score.

➢ Regarding score for irreversible element

We gave a score of GV colored in green was max score of 10 and a score of GV colored in gold was min score of 0 based on the following thinking:

Max reversible condition: the condition that “the GV metric values are 0 during nighttime in almost patients and GV metric values exceed 0 during daytime in some patients” occurs with the highest possibility among the above metrics. (Score 0)

Max irreversible condition: chronological differences of GL (Score 10)

Second irreversible condition: the condition that “the GV metric values exceed 0 during nighttime in some patients and GV metric values are 0 during daytime in almost patients” occurs with the highest possibility among the above metrics. (Score 7)

We gave a score of 3 to normal quantitative variable (Q element) as a middle of max reversible condition (Score 0) and second irreversible condition (Score 7).

We gave a score of 4 to GVs colored in yellow and skin color as a judge of having a little bit stronger irreversible element compared to normal quantitative variable.

P.S. How about the MD for other GV?

CV of patients with mean GV correlated to MD (r=–0.66, p<0.001) (n=30).

MD varies among GV, depending on CV of patients with mean GV.

GV metrics are roughly classified into 3 group by calculation element of which the formula consists.

Category element (C): In calculation process, glucose levels (GL) convert to 0 or 1.

Quantitative element (Q): GV metric values remain quantitative data.

Having both elements (B): In calculation process, GL partly convert to 0 and the other GL are used to calculate GV metric values which remain quantitative data.

➢ High CV (of patients with mean GV) element:
Frequent 0, B, C, Logarithm, Hypermax (max of hyperglycemia risk)+Hypomax (max of hypoglycemia risk), Low denominator

➢ Element keeping ranks:
Chronological difference variability, Averaging

☆GV metrics are further classified by color according to the characteristics below. (my opinion)

GV: The proportion of “0” is high. B or C element. The fact that hypoglycemia mainly occurs during nighttime have already almost made the rank among patients irreversible at ED of 0:00–09:40. These make change of rank among patients difficult.

GV: Accumulating differences between close timepoint chronologically is easy to make irreversible magnitude relationship among patients because “CV of ‘chronological differences of GL’ (‘CD’)” (“CDCV”) is much higher than “CV of GL” (CV). This is because “numerator” is close in both and denominator for CDCV is quite lower than that for CV. [Chronological difference variability]

GV: Normal quantitative variable (Q element) with quite low CVEDGV

GV: B or C element. The proportion of “0” is lower than the GV colored in blue. When GV values change from 0 to >0, the ranks among patients be sure to change. This is more frequent than the GV colored in blue.

GV: High CV of patients with high CV of ED GV (CVEDGV) due to logarithm and Hypermax+Hypomax

GV: Normal quantitative variable. In general, CV of ED variability is higher than CV of ED mean.

GV: B or C element. CV of ED TAR>250 is easy to be enhanced as values because the GV values are almost 0 during nighttime and extreme hyperglycemia occurs during daytime. This makes change of rank among patients easy. IGC (Hypoglycemic Index, Hyperglycemic Index) is the easiest to vary among the metrics shown left because “absolute values deviating from threshold” (deviating values) convert higher risks as values than the other hyper- or hypoglycemic metrics. This is because, in IGC, deviating values are averaged by the number of those, though, in the others, those are averaged by the number of all glucose levels (low denominator).

GV: Normal quantitative variable with high CVEDGV due to rank values (Averaging makes CVEDGV lower).

We created the simulation data to investigate the greened characteristic.

➢ The GL1 and GL2 were created intending the below purpose.

1. Mean, SD and CV over total duration are identical between GL1 and GL2 and between GLD1 and GLD2.
2. Making a difference between GLD1 and GLD2 early

To achieve the above purpose, simulated GL were arranged in a crossover as shown.

Chronological differences (CD) are directly independent from mean GL [MGL] (indirectly relevant), however, SD depends on MGL. Thus, compared to CD, SD is easy to reverse magnitude relationship.

High CDCV is easy to make large magnitude relationship of GV, which also makes high variability of magnitude relationship, between patients. As a characteristic of averaging, more proceeding averaging GLD over time leads to lower variability of averaged GLD. Thus, It is difficult to reverse the difference once made. This is a characteristic of CD.

Time	GL1	GLD1	GL2	GLD2
0:00	200	50	200	50
0:05	150	50	150	50
0:10	100	50	150	0
0:15	150	50	100	50
0:20	200	50	100	0
0:25	150	50	150	50
0:30	100	50	200	50
0:35	150	50	150	0
0:40	200	50	150	50
0:45	150	50	150	0
0:50	150	0	200	50
0:55	100	50	150	50
1:00	100	0	150	50
1:05	150	50	150	50
1:10	200	50	200	50
1:15	200	0	150	50
1:20	150	50	100	50
1:25	150	0	150	50

D of mean of GL	D of SD of GL	D of mean of GLD	D of SD of GLD	ED from 0:00	E mean	E SD	E CV	E mean	E SD	E CV	E mean	E SD	E CV	E mean	E SD	E CV
-16.7	21.1	25.0	-35.4	10.0	150.0	50.0		50.0	0.0		166.7	28.9		25.0	35.4	
0.0	0.0	16.7	-28.9	15.0	150.0	40.8		50.0	0.0		150.0	40.8		33.3	28.9	
20.0	0.0	25.0	-28.9	20.0	160.0	41.8		50.0	0.0		140.0	41.8		25.0	28.9	
16.7	0.0	20.0	-27.4	25.0	158.3	37.6		50.0	0.0		141.7	37.6		30.0	27.4	
0.0	0.0	16.7	-25.8	30.0	150.0	40.8		50.0	0.0		150.0	40.8		33.3	25.8	
-6.3	-3.9	21.4	-26.7	35.0	150.0	37.8		50.0	0.0		156.3	41.7		28.6	26.7	
0.0	0.0	18.8	-25.9	40.0	155.6	39.1		50.0	0.0		155.6	39.1		31.3	25.9	
0.0	0.0	22.2	-26.4	45.0	155.0	36.9		50.0	0.0		155.0	36.9		27.8	26.4	
-4.5	-2.5	15.0	-10.0	50.0	154.5	35.0		45.0	15.8		159.1	37.5		30.0	25.8	
-8.3	1.0	13.6	-10.2	55.0	150.0	36.9		45.5	15.1		158.3	35.9		31.8	25.2	
-7.7	0.0	8.3	-5.2	60.0	146.2	38.0		41.7	19.5		153.8	38.0		33.3	24.6	
-7.1	0.0	7.7	-5.2	65.0	146.4	36.5		42.3	18.8		153.6	36.5		34.6	24.0	
-6.7	0.6	7.1	-5.3	70.0	150.0	37.8		42.9	18.2		156.7	37.2		35.7	23.4	
-3.1	2.7	3.3	-2.2	75.0	153.1	38.6		40.0	20.7		156.3	35.9		36.7	22.9	
0.0	0.0	3.1	-2.2	80.0	152.9	37.4		40.6	20.2		152.9	37.4		37.5	22.4	
0.0	0.0	0.0	0.0	85.0 (Total)	152.8	36.3	23.7	38.2	21.9	57.2	152.8	36.3	23.7	38.2	21.9	57.2
P/N change	P/N change	No P/N change	No P/N change	Mean	152.8	38.8					153.7	37.6				
				SD	3.9	3.5					6.4	3.1				
				CV	2.5	9.0					4.1	8.2				

GLD: Consecutive GL difference, E mean: Extracted mean,
ED from 0:00: Extracted duration from 0:00,
P/N change: Positive/Negative change,
D of mean of GL: Difference of mean of GL (GL1-GL2),
RD of mean of GL: Relative difference of mean of GL [GL1-GL2]/GL2]

“numerator” is close in both

denominator for CDCV is quite lower than that for CV

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☆ The results obtained using the present study design method to estimate 24h–GV (“R^2=0.9”) are practically useful for GV metrics whose formula consists of “category element” (shown as “C” in the upper center table) because patients can categorize GL visually in personal CGM.

☆ The 67.4% (16:00) obtained in the present study is specific to TIR70-180.