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Hypoglycemia prediction from the coefficient of variation for each HbA1c value

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INTRODUCTION

- It has also been reported that the coefficient of variation (CV) corresponding to the number of hypoglycemia cases decreases as HbA1c values decrease [1].
- When an association between the CV and hypoglycemia is considered, the possibility that the CV varies according to HbA1c values should be considered.
- If hypoglycemia can be predicted from both HbA1c values and the CV, the relationship between glycemic variability and hypoglycemia can be assessed in detail.
- We studied a formula that could predict hypoglycemia based on HbA1c values and the CV.

1. McQueen RB et al. ADA 2021; ePoster: 59-LB.

MATERIALS AND METHODS

- This was a prospective observational study. One hundred and one outpatients with type 2 diabetes mellitus underwent HbA1c testing, wore a flash glucose monitor (FGM: FreeStyle Libre Pro, Abbott Diabetes Care, Alameda, CA, USA), and did not change diabetic treatment, on a hospital visit.
- The CV and mean glucose levels were calculated using the FGM data over 24-h × 13 days.
- The glucose management indicator (GMI) was calculated using the mean glucose levels, and we compared the GMI to the HbA1c values mainly to detect differences between sensor glucose levels (SG) and blood glucose levels. It has been previously reported that the HbA1c value minus (–) GMI >0.5% is associated with the risk of hypoglycemia, and the GMI – HbA1c value >0.5% is associated with the risk of hyperglycemia [2]. Therefore, we assessed the difference between the GMI and HbA1c value with real numbers.
- We calculated the "percentage of mean absolute deviation to mean glucose levels" (Metric1) as a new metric.

2. Toschi E, et al. Diabetes Care. 2020; 43:2349-54.

- Primary endpoints
  - CVs corresponding to HbA1c values (ΔA1c [GMI – HbA1c value] was fixed to 0) for the optimal predicted value for the logistic regression analysis when the response variable was hypoglycemia absence and the explanatory variables were the CV, HbA1c value, and ΔA1c.
- Secondary endpoints
  - Predicting hypoglycemia absence and severe hypoglycemia absence from the CV, HbA1c value, and ΔA1c using the multiple logistic regression analysis.
  - CVs corresponding to the HbA1c value (ΔA1c was fixed to 0) for the optimal predicted value for the logistic regression analysis when the response variable was severe hypoglycemia absence and the explanatory variables were the CV, HbA1c value, and ΔA1c.
  - Predicting Metric 1 from the CV using the univariate linear regression analysis.

Characteristic	Values
N (Male / Female)	101 (61 / 40)
Age, years	69.3 ± 13.6
BMI, kg/m^2	24.3 ± 4.1
HbA1c, %	8.0 ± 1.5
GMI, %	7.3 ± 1.1
ΔA1c, %	-0.7 ± 1.0
CV, %	30.7 ± 7.6
Hypoglycemia, n (%)	49 (48.5)
Severe hypoglycemia, n (%)	23 (22.8)
Metric 1, %	25.1 ± 6.3

Data are shown as mean ± standard deviation.

How to calculate CV from PV, HbA1c, and ΔA1c?

$$\frac{y = 1 \div (1+e^{-(ax_1+bx_2+cx_3+d)})}{1 + e^{-(ax_1+bx_2+cx_3+d)} = \frac{1}{y}}$$

$$e^{-(ax_1+bx_2+cx_3+d)} = \frac{1}{y} - 1$$

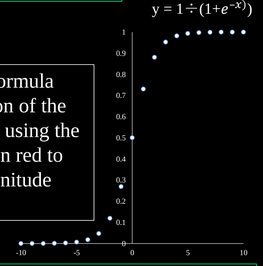
$$\mathrm{LN}(e^{-(ax_1+bx_2+cx_3+d)}) = \mathrm{LN}(\frac{1}{y} - 1)$$

$$-ax_1 - bx_2 - cx_3 - d = \mathrm{LN}(\frac{1}{y} - 1)$$

$$-bx_2 - cx_3 - d - \mathrm{LN}(\frac{1}{y} - 1) = ax_1$$

$$(-bx_2 - cx_3 - d - \mathrm{LN}(\frac{1}{y} - 1)) \div a = x_1$$

- The underlined formula intends conversion of the values calculated using the formula painted in red to 0–1 keeping magnitude relationship.



- If x_2 of HbA1c, x_3 of ΔA1c, constant term, and y of optimal PV are substituted to the formula painted in light blue, x_1 of CV can be calculated.
- If coefficients of explanatory variables, constant term, and optimal PV for logistic regression analysis can be calculated from statistical analysis software, the explanatory variable can be calculated from optimal PV and the other explanatory variables using Excel normal functions with the formula painted in light blue.

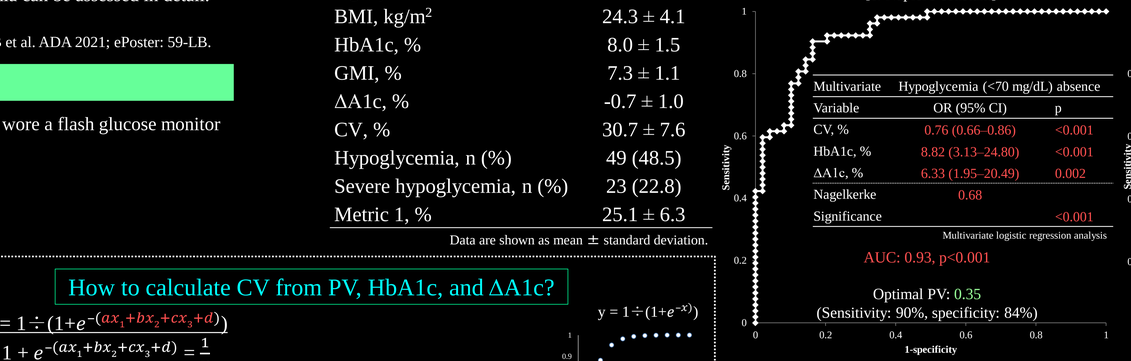
- The CV correlated with Metric1 (r=0.99, p<0.001, Metric1=0.82 × CV–0.006 [formula1]).

RESULTS

Hypoglycemia (<70 mg/dL) absence n=101 Severe hypoglycemia (<54 mg/dL) absence

ΔA1c: glucose management indicator (GMI) – HbA1c

Predicted values (PV)=1 ÷ (1+e$^{(-0.28\times CV+2.18\times HbA1c+1.85\times \Delta A1c-7.48)}$)
[e: Napier's constant]



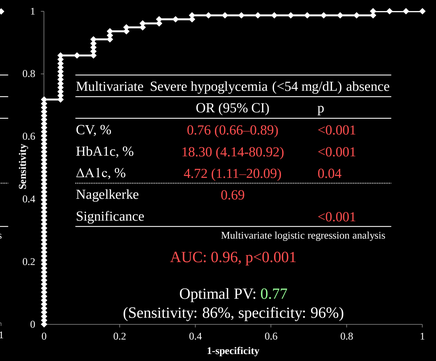
Multivariate	Hypoglycemia (<70 mg/dL) absence	
Variable	OR (95% CI)	p
CV, %	0.76 (0.66–0.86)	<0.001
HbA1c, %	8.82 (3.13–24.80)	<0.001
ΔA1c, %	6.33 (1.95–20.49)	0.002
Nagelkerke	0.68	
Significance		<0.001

Multivariate logistic regression analysis

AUC: 0.93, p<0.001

Optimal PV: 0.35
(Sensitivity: 90%, specificity: 84%)

PV=1 ÷ (1+e$^{(-0.27\times CV+2.91\times HbA1c+1.55\times \Delta A1c-10.66)}$)



Multivariate	Severe hypoglycemia (<54 mg/dL) absence	
	OR (95% CI)	p
CV, %	0.76 (0.66–0.89)	<0.001
HbA1c, %	18.30 (4.14-80.92)	<0.001
ΔA1c, %	4.72 (1.11–20.09)	0.04
Nagelkerke	0.69	
Significance		<0.001

Multivariate logistic regression analysis

AUC: 0.96, p<0.001

Optimal PV: 0.77
(Sensitivity: 86%, specificity: 96%)

Hypoglycemia (<70 mg/dL) absence

0.35 =1 ÷ (1+e$^{(-0.28\times CV+2.18\times HbA1c+1.85\times \Delta A1c-7.48)}$)

Severe hypoglycemia (<54 mg/dL) absence

0.77 =1 ÷ (1+e$^{(-0.27\times CV+2.91\times HbA1c+1.55\times \Delta A1c-10.66)}$)

ΔA1c = 0%

HbA1c, %	CV, %	
	Hypoglycemia (<70 mg/dL) absence	Severe hypoglycemia (<54 mg/dL) absence
6	22.0	20.6
6.5	25.9	26.0
7	29.8	31.4
7.5	33.6	36.8
8	37.5	42.1
8.5	41.4	47.5
9	45.3	52.9
9.5	49.1	58.3
10	53.0	63.7

DISCUSSIONS

- The threshold of the CV for predicting hypoglycemia corresponding to a HbA1c value of 8% (37.5%) was close to the threshold of the CV for the risk of hypoglycemia (36%) under the condition where the HbA1c value of patient characteristics was 7–8% [3], which was referred to as a key threshold of CV in the CGM data analysis in the international consensus [4].
- It has been reported that real-time CGM (Dexcom G6) can improve the "time in range" more than intermittently scanned CGM (FreeStyle Libre) [5]. The use of alarm functions may contribute to the previous study results.
- Moreover, different glucose thresholds for hypoglycemia and hyperglycemia alarms for real-time CGM have been previously reported to be associated with various hypoglycemia and hyperglycemia outcomes [6]. Thus, it is important to determine whether alarm functions are used, and whether an alarm threshold is appropriate for achieving target glycemic variability.

3. Monnier L, et al. Diabetes Care. 2017; 40:832-8. 4. Danne T, et al. Diabetes Care. 2017; 40:1631-40.
5. Visser MM, et al. Lancet. 2021; 397:2275-83. 6. Lin YK, et al. J Endocr Soc. 2019; 4:bvz005.

CONCLUSION

- The CV should be reduced more to prevent hypoglycemia as HbA1c values decrease.
- For avoiding hypoglycemia, an "alarm threshold using 'mean glucose levels (Mean) corresponding to the HbA1c values', and 'Metric 1 corresponding to the CV calculated using formula 1' " (Mean ± Mean × Metric 1 ÷ 100) should be used for personal continuous glucose monitoring, and all glucose levels should be kept within the alarm threshold.

CONTACT INFORMATION

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