The Relationship Between CGM-Derived Metrics, A1C, and Risk of Hypoglycemia in Older Adults With Type 1 Diabetes

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OBJECTIVE

Continuous glucose monitoring (CGM) is now commonly used in the management of type 1 diabetes (T1D). The CGM-derived coefficient of variation (CV) measures glucose variability, and the glucose management indicator (GMI) measures mean glycemia (previously called estimated A1C). However, their relationship with laboratory-measured A1C and the risk of hypoglycemia in older adults with T1D is not well studied.

RESEARCH DESIGN AND METHODS

In a single-center study, older adults (age ≥65 years) with T1D wore a CGM device for 14 days. The CV (%) and GMI were calculated, and A1C and clinical and demographic information were collected.

RESULTS

We evaluated 130 older adults (age 71 ± 5 years), of whom 55% were women, 97% were White, diabetes duration was 39 ± 17 years, and A1C was 7.3 ± 0.6% (56 ± 15 mmol/mol). Participants were stratified by high CV (>36%; $n = 77$) and low CV (≤36%; $n = 53$). Although there was no difference in A1C levels between the groups with high and low CV (7.3% [56 mmol/mol] vs. 7.3% [53 mmol/mol], $P = 0.4$), the high CV group spent more time in hypoglycemia (<70 mg/dL and ≤54 mg/dL) compared with the group with low CV (median 31 vs. 84 min/day, $P < 0.0001$; 8 vs. 46 min/day, $P < 0.001$, respectively). An absolute difference between A1C and GMI of ≥0.5% was observed in 46% of the cohort. When the A1C was higher than the GMI by ≥0.5%, a higher duration of hypoglycemia was observed ($P = 0.02$).

CONCLUSIONS

In older adults with T1D, the use of CGM-derived CV and GMI can better identify individuals at higher risk for hypoglycemia compared with A1C alone. These measures should be combined with A1C for better diabetes management in older adults with T1D.

Older adults with type 1 diabetes (T1D) are at a higher risk of hypoglycemia and its associated negative consequences, such as loss of consciousness, cardiac arrhythmias, traumatic falls, and higher risk of mortality (1–5). Current guidelines for older adults with T1D recommend less stringent hemoglobin A_{1c} (A1C) targets to mitigate hypoglycemia (6). However, studies have shown that liberalization of A1C may not protect against the risk of hypoglycemia in the older population (1,7–9). Additionally, comorbidities that affect red blood cell (RBC) life span, such as anemia, chronic kidney

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disease, and acute illnesses, are more common in the older population and can lead to an unreliable interpretation of A1C (10,11). Thus, additional measures to assess hypoglycemia risk and glycemic control are needed to care for older adults with diabetes.

Continuous glucose monitoring (CGM) has been shown to be a better tool to capture glucose average, glucose trends, glucose variability, and time spent in hypoglycemia compared with A1C (12). A recent CGM consensus statement recommended the coefficient of variation (CV) percentage, calculated as the (SD of glucose/mean glucose level) × 100, as a measure to evaluate glucose variability and risk of hypoglycemic excursions (11). The recommended threshold for CV is defined as stable (CV ≤36%) and unstable (CV > 36%) (13). The lower CV number suggests less glucose variability, while the higher CV number suggests more glucose variability. Another CGM-derived measure coined, "glucose management indicator" (GMI), reflects the mean glucose level based on at least 14 days of CGM data (14). This measure aims to mitigate confusion between CGM-derived average glucose, the "estimated A1C," and laboratory-measured A1C, which measures the average glucose over the prior 3 months. The formula to calculate GMI was developed using a large cohort of people with type 1 and type 2 diabetes. However, older adults with T1D made up only 6% of this cohort (14).

Although CGM and its derived metrics—CV and GMI—are now being used more frequently in adults with T1D, there are limited data available on the use of these metrics in the older population with T1D. In this study, we evaluated a well-characterized cohort of older adults with T1D to understand the relationship among CGM-derived measures of CV, GMI, time spent in hypoglycemia, and laboratory A1C.

RESEARCH DESIGN AND METHODS

We performed a post hoc analysis of baseline data from the ongoing Technological Advances in Glucose Management in Older Adults (TANGO) study assessing the use of CGM in older adults with T1D (Clinicaltrials.gov NCT03078491). Data were collected between April 2017 and December 2019. Eligibility criteria included age ≥65 years and willingness and capability to use CGM. Exclusion criteria included allergies to the tape/adhesive used for CGM sensors, acetaminophen use, chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) <30 mL/min, or inability to use CGM. All participants provided written informed consent. The Joslin Diabetes Center Institutional Review Board approved the study protocol.

Demographic and medical information and clinical data on diabetes management were collected. Cognitive function (by the Montreal Cognitive Assessment [MoCA]) and depression (by Geriatric Depression Scale or reported as diagnosis) were assessed, and laboratory A1C and kidney function (eGFR) tests were performed on all participants (15,16). Survey measures for hypoglycemia unawareness (by the Clarke method) were also performed (17). Data on the insulin regimen was extracted for multiple daily injection (MDI) users from electronic medical records and a patient questionnaire. For insulin pump users, data were collected from pump downloads at the time of the CGM download.

A masked CGM device (Dexcom G4) was worn for 14 days by the participants who were CGM naive, whereas participants already using their own personal Dexcom CGM continued to use the device in real time and consented to having their personal device data downloaded by the study staff. All participants using a personal CGM device had been using it for at least 6 months before enrollment. CGM data were downloaded from a 2-week period; a minimum of 192 h of CGM data were required for inclusion in the study analyses.

The CV% was calculated as (SD of glucose/mean glucose level) × 100 (13). GMI percentage was calculated as 3.31 + (0.02392 × mean glucose in mg/dL) (14).

Definitions

Overall hypoglycemia was defined as sensor glucose <70 mg/dL. Clinically significant hypoglycemia was defined as sensor glucose ≤54 mg/dL (13). Nocturnal hypoglycemia was defined as duration of hypoglycemia between 10:00 P.M. and 6:00 A.M. in min/night or percentage of nighttime hours (8 h).

Hyperglycemia was defined as sensor glucose >250 mg/dL.

Time in range was defined as sensor glucose 70–180 mg/dL.

Cognitive dysfunction was defined as a MoCA score <26 (15). Hypoglycemia unawareness was defined as ≥4 responses rated as reduced awareness on the Clarke survey (17). The presence of depression was defined as a diagnosis of depression or a score of >5 on the Geriatric Depression Scale (16).

Statistical Analysis

Descriptive statistics for demographic and clinical data are reported as number (*n*) and percentage (%) of the cohort for categorical variables. For continuous variables, data are reported as mean ± SD for data with normal distribution and as median and first and third interquartile (quartile 1, quartile 3) for data with nonnormal distribution. SAS version 9.4 software was used for all analyses and included Pearson correlations, general linear models, Student *t* tests, and Fisher exact tests. A *P* value of 0.05 was considered statistically significant.

RESULTS

The study enrolled 130 older adults (mean age 71 ± 5 years; 55% were women, 97% were White) with T1D (mean duration of diabetes of 39 years). Overall, 38% of participants were on MDI, 62% were on insulin pump therapy, and 54% were using a personal CGM device. The characteristics of the overall cohort and stratified by low CV (≤36%) and high CV (>36%) are reported in Table 1.

In the whole cohort, the CV strongly correlated with the duration of glucose <70 mg/dL and ≤54 mg/dL, with a higher risk of hypoglycemia with a higher value of CV ($P < 0.0001$, $r = 0.66$, $\beta = 0.71$; $P < 0.0001$, $r = 0.7$, $\beta = 0.26$) (Fig. 1*A* and *B*, respectively). While 77 participants (59%) had high CV, 53 (41%) had low CV. The group with high CV spent more time in overall hypoglycemia compared with the group with low CV (median [quartile 1, quartile 3] 84 [47, 131] vs. 31 [9, 39] min/day, $P < 0.001$). Similarly, the group with high CV spent more time in clinically significant hypoglycemia range compared with the group with low CV (46 [11, 58] vs. 8 [1, 9] min/day, $P < 0.0001$). Nocturnally, the high CV group had more overall hypoglycemia (44 [11, 55] vs. 16 [0, 16] min/night, $P < 0.0001$) and more clinically significant hypoglycemia (20 [2, 21] vs. 3 [0, 3] min/night, $P < 0.0001$) compared

Table 1—Participant characteristics of the overall cohort and stratified by CV%

Participant characteristics	Total	CV ≤36%	CV >36%	*P* value
Participants	130	53 (41)	77 (59)	
Demographics				
Age (years)	71 ± 5	71 ± 4	71 ± 5	NS
Female	72 (55)	28 (53)	44 (57)	NS
Race (non-Hispanic White)	123 (97)	48 (94)	75 (96)	NS
BMI (kg/m^2)	26 ± 4	26 ± 4	25 ± 4	NS
Education (college diploma or higher)	119 (92)	48 (91)	72 (93)	NS
Living alone	24 (21)	8 (16)	16 (21)	NS
Total medications/day (*n*)	10 ± 5	10 ± 5	9 ± 4	NS
Comorbidities/medical conditions (*n*)	8 ± 4	9 ± 4	8 ± 4	NS
Cognitive dysfunction**	67 (51)	24 (45)	43 (56)	NS
Depression	48 (37)	18 (34)	30 (39)	NS
Diabetes characteristics				
Age at diagnosis (years)	33 ± 17	32 ± 18	33 ± 16	NS
Duration of diabetes (years)	39 ± 17	39 ± 18	38 ± 15	NS
Insulin administration				
Pump therapy	80 (62)	34 (64)	46 (59)	NS
MDIs	50 (38)	19 (36)	31 (40)	NS
Personal CGM use	70 (54)	41 (77)	29 (38)	**<0.00001**
Total insulin dose (units/day)	35 ± 18	36 ± 16	35 ± 19	NS
Basal insulin dose (% of total insulin dose)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	NS
A1C (%)	7.3 ± 0.6	7.3 ± 0.9	7.3 ± 0.8	NS
A1C (mmol/mol)	55 ± 15	53 ± 18	56 ± 12	NS
Participants with hypoglycemia unawareness	49 (45)	18 (44)	31 (46)	NS
Measures of health care use				
≥1 severe hypoglycemia events within the last year	19 (15)	7 (13)	12 (16)	NS
≥1 hospitalizations within last 3 months	3 (2)	1 (1)	2 (3)	NS
≥1 ED visits within the last 3 months	6 (5)	2 (4)	4 (5%)	NS

Values are mean ± SD or *n* (%). *P* value in boldface is statistically significant at $P < 0.05$. ED, emergency department. **MoCA score <26.

with the low CV group. Moreover, the group with high CV spent more time in hyperglycemia >250 mg/dL compared with the group with low CV (953 [739, 1,142] vs. 834 [741, 965] min/day, $P = 0.02$). Additionally, the group with high CV spent less time in range compared with the group with low CV (62 [21, 167] vs. 157 [80, 242] min/day, $P = 0.02$).

Interestingly, despite significant differences in hypoglycemia and hyperglycemia duration between the two groups, A1C values did not differ between the groups with high and low CV (7.3 ± 0.8% [56 ± 12 mmol/mol] vs. 7.3 ± 0.9% [53 ± 18 mmol/mol], respectively) (Table 2).

The groups with high and low CV did not differ in age, BMI, duration of diabetes, methods of insulin administration, total daily insulin dose, basal insulin dose, presence of hypoglycemia unawareness, history of severe hypoglycemia over the last 6 months, depression, or cognitive dysfunction. More participants in the group with low CV were using personal CGM compared with the group with high CV (41 [77%] vs. 29 [38%], $P < 0.00001$);

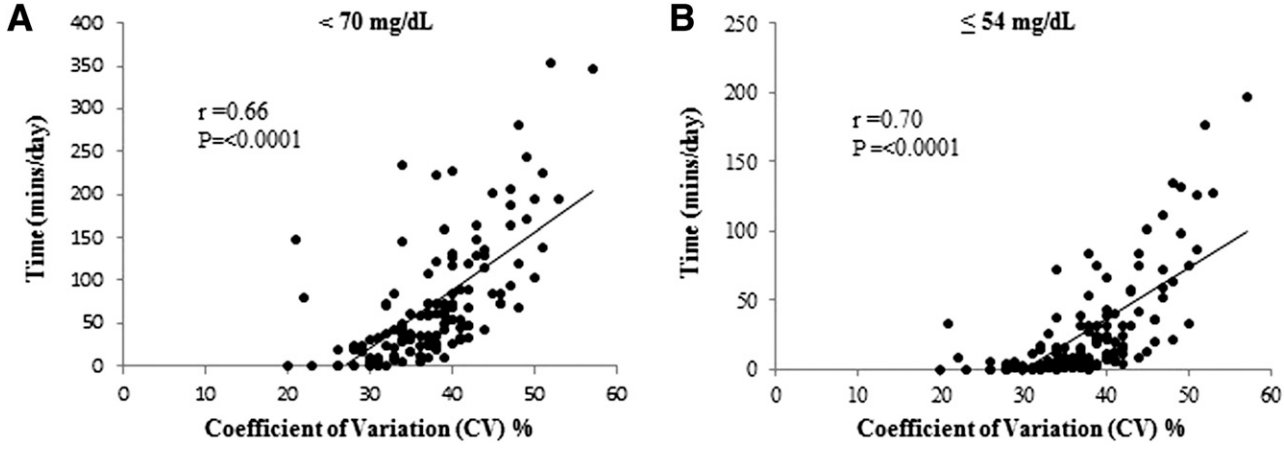

Figure 1—Relationship between CV% and time spent in hypoglycemia (min/day). Sensor glucose <70 mg/dL (*A*) and ≤54 mg/dL (*B*). Pearson correlation coefficient (*r*) and *P* value are shown in each panel.

Table 2—Glycemic metrics according to CV%

	CV ≤ 36%	CV > 36%	*P*
Participants	53 (41)	77 (59)	
A1C (%)	7.3 ± 0.9	7.3 ± 0.8	0.4
A1C (mmol/mol)	53 ± 18	56 ± 12	0.4
Time spent in hypoglycemia (min/day)			
<70 mg/dL	31 (9, 39)	84 (47, 131)	**<0.0001**
≤54 mg/dL	8 (1, 9)	46 (11, 58)	**<0.0001**
Nighttime (10:00 P.M. to 6:00 A.M.) time spent in hypoglycemia (min/day)			
<70 mg/dL	16 (0, 16)	44 (11, 55)	**<0.0001**
≤54 mg/dL	3 (0, 3)	20 (2, 21)	**<0.0001**
Time spent in range (min/day)			
70–180 mg/dL	953 (739, 1142)	834 (741, 965)	**0.02**
Time spent above range (min/day)			
>180 mg/dL	485 (265, 660)	491 (356, 610)	0.4
>250 mg/dL	62 (21, 167)	157 (80, 242)	**0.02**

Values are mean ± SD, median (quartile 1, quartile 3), or *n* (%). Values in boldface are statistically significant at $P < 0.05$.

however, use of a personal CGM did not affect the relationship between CV and duration of hypoglycemia.

Next, we evaluated the relationship between CGM-derived mean glucose as GMI and A1C in our cohort. An absolute difference between GMI and A1C of ≥0.5% (considered clinically significant) was present in 46% of participants, while an absolute difference of >1% was present in 16% of participants (Fig. 2). The difference between GMI and A1C remained after adjusting for the factors that may alter RBC life span, such as eGFR, recent acute illness, or visit to the emergency department within the prior 3 months.

Among the 46% ($n = 60$) of participants with an absolute difference between A1C and GMI of ≥0.5%, 63% ($n = 38$) had an A1C greater than the GMI, and 37% ($n = 22$) had an A1C lower than GMI. When the A1C value was greater than GMI by ≥0.5%, it correlated significantly with the duration of overall hypoglycemia and clinically significant hypoglycemia ($P = 0.03$, $r = 0.33$, $\beta = 4.13$; $P = 0.05$, $r = 0.35$, $\beta = 0.3$, respectively) but not with time in range and time spent in hyperglycemia. However, when the A1C value was lower than the GMI by ≥0.5%, it correlated significantly with time in range and time spent in hyperglycemia (>250 mg/dL) ($P = 0.009$, $r = 0.51$, $\beta = 160.8$; $P = 0.008$, $r = 0.52$, $\beta = 108.4$, respectively) but not with the duration of overall hypoglycemia and clinically significant hypoglycemia. Adjusting for personal CGM use, insulin administration method, or kidney function did not affect the results.

CONCLUSIONS

In this observational study, we found that CGM-derived metrics of CV and GMI provided important information regarding the risk of hypoglycemia, which was not identified solely by A1C levels in older adults with T1D. Although laboratory A1C provides mean glucose over a 3-month period, the CGM-derived metrics over 2 weeks can provide an important additional clinical tool for treatment decisions in the vulnerable older population with T1D at a high risk of poor outcomes with hypoglycemia.

Recently, to reduce the risk of hypoglycemia, the clinical target for time in range in older adults with T1D has been defined as ≥50%, with a goal of more time spent above range, since A1C may not capture time spent in hypoglycemia (18). Several studies have shown the inadequacy of A1C measurement alone, especially in the older population (4,9,19–22), because laboratory A1C does not capture short-term fluctuations of glucose levels (23) and does truly not reflect time spent in hypoglycemia (24). A case-control study of elderly people with T1D and a history of severe hypoglycemia also showed that glucose variability, rather than A1C, was associated with a longer duration of hypoglycemia (4). The results of our study underscore this point by showing that the A1C levels in the study participants did not differ between the group with high CV and greater time in hypoglycemia versus the group with lower CV and lesser time in hypoglycemia. The results also show a greater time spent in hyperglycemia in the group with high CV, confirming that CV, rather than A1C, captures short-term fluctuations in glucose levels. Thus, our results show the added value of having the CV measure in addition to A1C levels when managing older adults with T1D.

In our cohort, an increased risk of hypoglycemia with high CV persisted when accounting for the insulin administration method and insulin amount as total and basal daily dose. Whether the participants used MDI or an insulin pump, those with high CV had significantly more overall, clinically significant, and nocturnal hypoglycemia than their counterparts with low CV. We also showed that the number of older participants with high CV was lower in the group using personal CGM (41%) than in the group that did not use personal CGM (80%). These data support other studies showing lower glycemic variability in adults using a personal CGM (12,25,26). Additionally, in our cohort, hypoglycemia unawareness did not differ among participants with different levels of glucose variability. The participants with high CV, and thus at a higher risk of hypoglycemia, reported the same amount of hypoglycemia unawareness as those with low CV. Thus, wide glycemic excursions should be avoided in all older adults with T1D, and not just in the patients with a history of hypoglycemia unawareness. It also supports the need for an independent measure to assess the risk of hypoglycemia, such as CV, instead of self-report history of hypoglycemia.

Our study results also showed higher discrepancy between A1C and GMI in the

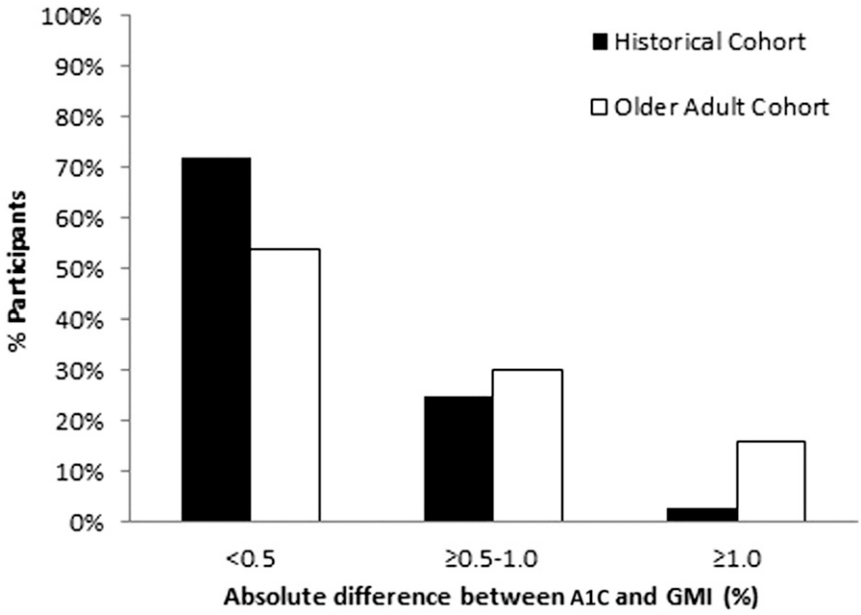

Figure 2—Absolute difference between A1C and GMI. Historical cohort vs. older adults with T1D.

older age group compared with the historical cohort described by Bergenstal et al. (14). In that cohort, only 15% of participants were >60 years of age, and only 34 older participants (6% of overall cohort) had T1D (14). Interestingly, in our cohort made up entirely of older adults with T1D, GMI differed from laboratory A1C much more than in the historical group. An absolute difference between A1C and GMI of ≥0.5% (considered clinically significant) was seen in 46% of our cohort compared with 28% in the historical cohort, while a difference of >1% was observed in 16% of older adults with T1D in our cohort compared with only 3% in the historical cohort (14). This finding is consistent with data in the literature that have shown that older adults have a much greater discrepancy between laboratory A1C and mean glucose (estimated A1C) derived by CGM data (4,19). This finding shows the need for more studies with a focus on older adults investigating the use of A1C as a guide for diabetes management as well as further investigation into the factors that may be affecting A1C values with aging. In the current study, a positive difference between laboratory A1C and GMI, meaning A1C is higher than GMI by ≥0.5%, was associated with a greater risk for total and clinically significant hypoglycemia. A negative difference between A1C and GMI, meaning A1C was lower than GMI by ≥0.5%, was associated with a greater time spent in hyperglycemia. These results may help clinicians identify patients at potential greater risk of hypoglycemia (those with A1C ≥0.5% above GMI) and hyperglycemia (those with A1C ≥0.5% below GMI) and guide clinical therapeutic decisions based on a combination of A1C and GMI.

The strengths of our study include the use of CGM in a large, well-phenotyped cohort of older adults with T1D with a long duration of diabetes, the largest described so far to our knowledge in a single-center study. Our cohort included participants who were naive to CGM as well as those who were using a personal CGM device prior to study participation. Thus, we were able to report that the relationship between CV and hypoglycemia risk, as well as the A1C similarities between groups, persisted when accounting for the glucose monitoring method.

One of the limitations of our study is the homogeneous Caucasian population from the northeast U.S., with a large number of highly educated participants. We also did not have information regarding all factors that may affect RBC life span and may impact the relationship between A1C and GMI.

Overall, this study shows that CGM-derived metrics, such as CV and GMI, are a helpful adjunct to A1C to guide clinicians to identify and potentially reduce the risk of time spent in hypoglycemia in older adults with T1D. This study is, to our knowledge, the first large study describing CGM-derived metrics and their relationship with laboratory A1C and hypoglycemia in older adults with T1D, underscoring the added value of use of CGM in older adults. Our results also show that data from the general adult population may not always apply to or match those in the older population. With the increasing use of technology, particularly CGM, more studies are needed focusing on older adults to integrate findings from CGM data with A1C to improve clinical outcomes in this vulnerable population with unique challenges.

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