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The Association of High and Low Glycation With Incident Diabetic Retinopathy in Adults With Type 1 Diabetes

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Abstract

Background: We investigated the risk of incident diabetic retinopathy (DR) among high glycator compared to low glycator patients based on the hemoglobin glycation index (HGI). Visit-to-visit variations in HGI also were assessed.

Methods: Glycated hemoglobin (HbA_{1c}) and continuous glucose monitoring data were collected up to 7 years prior to the date of eye examination defining incident DR or no retinopathy (control). Hemoglobin glycation index was calculated as difference in measured HbA_{1c} and an estimated A_{1c} from sensor glucose (eA_{1c}) to define high ($HbA_{1c} - eA_{1c} > 0\%$) or low ($HbA_{1c} - eA_{1c} < 0\%$) glycator. Stable glycators were defined as ≥75% of visits with same HGI category. Logistic regression was used to assess the association between glycation category and incident DR.

Results: Of 119 adults with type 1 diabetes (T1D), 49 (41%) were stable low glycator ($HbA_{1c} - eA_{1c} < 0\%$), 36 (30%) were stable high glycator ($HbA_{1c} - eA_{1c} > 0\%$), and 34 (29%) were unstable glycator. Using alternate criteria to define high vs low glycator (consistent difference in $HbA_{1c} - eA_{1c}$ of $> 0.4\%$ or $< 0.4\%$, respectively), 53% of the adults were characterized as unstable glycator. Compared to low glycators, high glycators did not have a significantly higher risk for incident DR over time when adjusted for age, T1D duration and continuous glucose monitoring (CGM) sensor type (odds ratio [OR] = 1.31, 95% confidence interval [CI] = 0.48-3.62, $P = .15$).

Conclusions: The risk of diabetic retinopathy was not found to differ significantly comparing high glycators to low glycators in adults with T1D. Moreover, $HbA_{1c} - eA_{1c}$ relationship was not stable in nearly 30% to 50% adults with T1D, suggesting that discordance in HbA_{1c} and eA_{1c} are mostly related either HbA1c measurements or estimation of A1c from sensor glucose rather than physiological reasons.

Keywords
diabetic retinopathy, glycator, HbA_{1c}, type 1 diabetes

Introduction

The discordance between measured glycated hemoglobin (HbA_{1c}) and A1c estimated (eA_{1c}) from either sensor glucose or fructosamine level is well-known.[1,2] As glycation of hemoglobin is non-enzymatic and considered to be regulated by genes,[3,4] it has been recognized that some people may have higher or lower HbA_{1c} than others at the same mean glucose levels. For example, African Americans have 0.4% to 0.5% higher HbA_{1c} at similar mean glucose than non-Hispanic whites.[5] A meta-analysis of 12 studies involving 49 238 individuals without diabetes, HbA_{1c} was significantly higher among blacks (by 0.26%), and Asians of Indian and Pakistan origin (by 0.24%) without much difference in Latino population (by 0.08%) compared to non-Hispanic whites at similar fasting plasma glucose levels.[6] Moreover, the discordance between mean glucose and HbA_{1c} is also common among non-Hispanic whites. In the DCCT trial

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where most participants with type 1 diabetes (T1D) were non-Hispanic whites, 57% of participants had discordance between laboratory measured HbA_{1c} and estimated A1c (eA_{1c}) based on mean glucose.[7]

Many methods have been described to study such discordance, eg, hemoglobin glycation index (HGI) (difference between measured HbA_{1c} and eA_{1c}),[7] a glycation gap (difference between the measured HbA_{1c} and that predicted by the fructosamine concentration),[8] or a glycation index (ratio of HbA_{1c} to 28-day rolling mean blood glucose).[9]

Few studies have suggested a higher risk for diabetes complications among high glycators (measured HbA_{1c} is higher than eA_{1c}) compared to low glycators (measured HbA_{1c} is lower than eA_{1c}).[7,8,10,11] However, this theory has been debated by others.[12,13] The clinical implication of the glycation gap and its risk with diabetes complications is currently unknown.

In this article, we investigated the visit-to-visit variation in the relationship between measured HbA_{1c} and eA_{1c} in adults with T1D and the association between high vs low glycator and risk for incident diabetic retinopathy (DR).

Methods

Study Design and Participants

A previously published cohort was used for the current analysis.[14] In brief, adults with T1D and incident DR group (defined as presence of DR from at least one retinal examination during the study inclusion period with the two consecutive previous retinal examinations without DR) and without DR (control group) were identified from electronic medical records (EMRs) between June 2018 and March 2022. Their continuous glucose monitoring (CGM) data and HbA_{1c} measurements were retrieved up to 7 years before the diagnosis of retinopathy. For each participant, raw CGM data were collected in CSV format for up to 90 days at each clinic visit performed after January 1, 2013, and prior to the date of diagnosis of retinopathy for the cases or the date of the last visit in the inclusion period for controls. From the visits over the same period, HbA_{1c} measurements (point-of-care or venous) were collected from the EMR. The detailed description of inclusion and exclusion, definition of retinopathy, and CGM data collection methods have been described previously.[14]

For this analysis, we used the individuals from the original cohort who had at least two clinic visits with non-missing HbA_{1c} and sufficient CGM data to calculate mean glucose. Sufficient CGM data was defined as at least 70% of data available in the 28 days prior to the visit date.

Statistical Analysis

Continuous variables were shown as mean ± standard deviation (SD), and categorical variables were shown as absolute numbers and percentages. We fit a linear regression model with mean glucose as the predictor and HbA_{1c} as the outcome. The model included a random intercept term to account for the correlation between measurements for the same participant. The intercept and slope from this model were used to calculate an estimated A1c (eA_{1c}) for each participant and visit. Hemoglobin glycation index was calculated as the difference in measured HbA_{1c} and an estimated A1c from sensor glucose (eA_{1c}) to define high ($HbA_{1c} - eA_{1c} > 0\%$) or low ($HbA_{1c} - eA_{1c} < 0\%$) glycator.

A participant was considered a stable (consistent) high glycator if they were classified as a high glycator ($HbA_{1c} - eA_{1c} > 0\%$) for at least 75% of visits (ie, consistently higher measured HbA_{1c} than expected from mean glucose). Similarly, a participant was considered a stable low glycator if they were classified as a low glycator ($HbA_{1c} - eA_{1c} < 0\%$) for at least 75% of visits. Otherwise, a participant was classified as "unstable" with respect to the HbA_{1c}-mean glucose relationship.

As a second estimation of glycation and stability, we used a 0.4% (clinically meaningful HbA_{1c} difference) cutoff for the difference between measured HbA_{1c} and eA_{1c}. $HbA_{1c} - eA_{1c} > 0.4\%$ and $< 0.4\%$ were considered high glycator and low glycator, respectively. Participants are considered stable if ≥75% of visits fall in the same category, otherwise, they are considered "unstable."

We used a logistic regression model to assess the association between DR and glycation profile (high/low glycator/unstable), after adjusting for age, T1D duration, and CGM sensor type. SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) was used for statistical analysis.

Results

First, we used a consistent difference in $HbA_{1c} - eA_{1c}$ of $>0\%$ or $<0\%$ to define high and low glycator, respectively. Using this definition, 49 adults with T1D (41%) were considered low glycator, and 36 (30%) were considered high glycator. The relationship between HbA_{1c} and eA_{1c} was not consistent in one direction for 34 adults (29%) who were characterized as unstable glycator. The baseline characteristics of adults with high glycation vs low glycation are provided in Table 1. There were no clinically meaningful differences in age, sex, race/ethnicity, and diabetes duration between high glycator and low glycator. Compared with the low glycator group (measured $HbA_{1c} - eA_{1c} < 0\%$), there was no significant increase in risk for incident DR among the high glycator group, in both unadjusted (odds ratio [OR] = 1.19, 95% confidence interval [CI] =0.50-2.83, $P = .32$) and adjusted models for age, T1D duration, and CGM sensor type (OR = 1.31, 95% CI = 0.48-3.62, $P = .15$).

Using alternate criteria to define high vs low glycator (consistent difference in $HbA_{1c} - eA_{1c}$ of $>$ or $<0.4\%$, respectively), 53% of the adults were characterized as unstable glycator. Only 13 adults (11%) were stable low glycator

Table 1. Patient Characteristics at Time of Study Inclusion.

	Overall (N = 119)	Low glycator (N = 49)	High glycator (N = 36)	Unstable (N = 34)
Age (years)				
Mean ± SD	34 ± 16	34 ± 15	36 ± 19	32 ± 15
Range	14 to 81	17 to 73	14 to 81	17 to 72
Sex				
Female *n (%)*	58 (49%)	26 (53%)	16 (44%)	16 (47%)
Male *n (%)*	61 (51%)	23 (47%)	20 (56%)	18 (53%)
Race/ethnicity				
Non-Hispanic white *n (%)*	97 (82%)	40 (82%)	28 (78%)	29 (85%)
Other *n (%)*	10 (8%)	4 (8%)	4 (11%)	2 (6%)
Unknown *n (%)*	12 (10%)	5 (10%)	4 (11%)	3 (9%)
Health insurance				
Private *n (%)*	101 (85%)	43 (88%)	27 (75%)	31 (91%)
Medicaid *n (%)*	15 (13%)	4 (8%)	8 (22%)	3 (9%)
Military plan *n (%)*	2 (2%)	1 (2%)	1 (3%)	0 (0%)
Unknown *n (%)*	1 (<1%)	1 (2%)	0 (0%)	0 (0%)
BMI (kg/m^2)				
Mean ± SD	26 ± 4	26 ± 4	25 ± 3	26 ± 5
Underweight (<18.5 kg/m^2) *n (%)*	1 (<1%)	0 (0%)	0 (0%)	1 (3%)
Normal weight (18.5 to <25.0 kg/m^2) *n (%)*	41 (34%)	17 (35%)	16 (44%)	8 (24%)
Overweight (25.0 to <30.0 kg/m^2) *n (%)*	42 (35%)	19 (39%)	8 (22%)	15 (44%)
Obese (≥30.0 kg/m^2) *n (%)*	15 (13%)	7 (14%)	3 (8%)	5 (15%)
Missing *n (%)*	20 (17%)	6 (12%)	9 (25%)	5 (15%)
Duration of T1D (years)				
Mean ± SD	18 ± 8	18 ± 8	19 ± 9	18 ± 7
Range	5 to 47	5 to 47	7 to 44	8 to 40

Consider the following categories: low glycator (measured HbA_{1c} − estimated $HbA_{1c} < 0\%$), high glycator (measured HbA_{1c} − estimated $HbA_{1c} > 0\%$). Participants are stable if ≥75% of visits fall in the same category, otherwise they are considered "unstable."
BMI, body mass index; SD, standard deviation; T1D, type 1 diabetes.

Table 2. Frequency of Stable and Unstable Glycators Using Two Different Methods.

Main definition[a]	Overall (N = 119)	DR group (N = 49)	Control group (N = 70)
Stable low glycator	49 (41%)	21 (43%)	28 (40%)
Stable high glycator	36 (30%)	17 (35%)	19 (27%)
Unstable	34 (29%)	11 (22%)	23 (33%)
Alternate definition[b]			
Stable low glycator	13 (11%)	5 (10%)	8 (11%)
Stable between −0.4 to 0.4	35 (29%)	12 (24%)	23 (33%)
Stable high glycator	8 (7%)	5 (10%)	3 (4%)
Unstable	63 (53%)	27 (55%)	36 (51%)

[a]Consider the following categories: stable low (measured HbA_{1c} − eA_{1c} <0%), stable high (measured HbA_{1c} − eA_{1c} >0%). Participants are stable if ≥75% of visits fall in the same category, otherwise they are considered "unstable."
[b]Consider the following categories: stable low (measured HbA_{1c} − eA_{1c} < -0.4%), stable between −0.4% and 0.4%, and stable high (measured HbA_{1c} − eA_{1c} > 0.4%). Participants are stable if ≥75% of visits fall in the same category, otherwise they are considered "unstable."

(measured − estimated HbA_{1c} <-0.4%) and eight (7%) were stable high glycator (measured − estimated HbA_{1c} >0.4%) (Table 2). Using this criteria, there was no significant increase in risk for incident DR among high glycator group (measured HbA_{1c} − eA_{1c} >0.4%) compared to low glycators (measured HbA_{1c} − eA_{1c} <−0.4%), in both unadjusted (OR = 2.67, 95% CI = 0.43-16.39, $P = .20$) and adjusted models for age, T1D duration, and CGM sensor type (OR = 1.39, 95% CI = 0.18-10.75, $P = .59$). Visit-to-visit variation in measured HbA_{1c} and eA_{1c} for each participant is shown in Figure 1.

Discussion

Using real-life, longitudinal data, we did not find a significant association between high glycators and incident DR in adults with T1D. This is in contrast to the analysis by McCarter and colleagues who analyzed DCCT data and reported a threefold increased risk for retinopathy among high glycators compared to low glycators.[7] However, that study had many major limitations. For example, they used only 1 day 7-point self-monitoring of blood glucose (SMBG) data to estimate

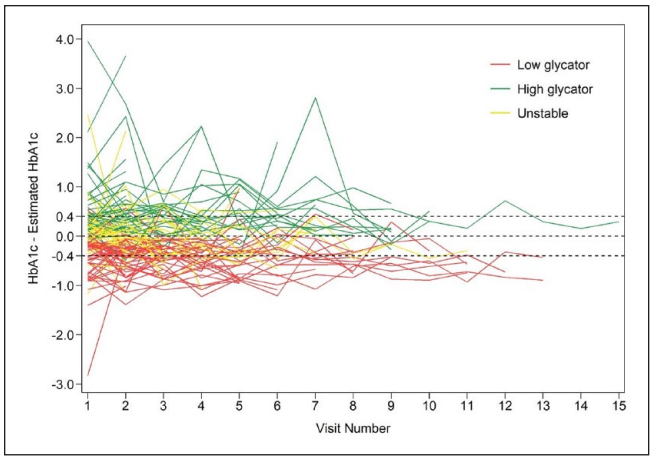

Figure 1. Spaghetti plot of difference between HbA_{1c} and eA_{1c} over time by participant.

A1c, which is insufficient compared with CGM data of our study. Lachin et al[12] used the same DCCT data and found a high correlation between HGI and HbA_{1c} and when the analysis was adjusted for HbA_{1c}, the association between HGI and retinopathy became insignificant suggesting that most of HGI risk was accounted for by HbA_{1c}. Moreover, Lachin argued that HGI may not represent the biological variation in glycation as the relationship between mean glucose and HbA_{1c} could be confounded by many factors such as red cell lifespan.

Our study found that nearly 30% of participants had an unstable relationship between measured HbA_{1c} and eA_{1c}; sometimes measured HbA_{1c} was higher than eA_{1c}, while other times, HbA_{1c} was lower than eA_{1c}. The percentage of participants with an unstable glycation gap increased when the glycation gap was defined as a consistent difference in HbA_{1c} and eA_{1c} of 0.4%. Thus, our data highlight that there are considerable visit-to-visit variations between measured HbA_{1c} and eA_{1c}. Previous literature is consistent with our results regarding the consistency and stability. Nayak et al[10] reported that only 549 of 1609 (34%) patients had consistently high or low glycation gaps in the repeated measures suggesting high discordance in the glycation directions between two visits. Thus, studies show 20% to 50% of people with diabetes do not have a consistent glycation profile. Therefore, HGI may not represent biological variation (genetic basis of non-enzymatic glycation) and the observed variation may represent the influence of various factors affecting either mean glucose (for eA_{1c}) or HbA_{1c} levels.

We believe that the variability/inconsistency of the calculation (measured $HbA_{1c} - eA_{1c}$) is mostly coming from the factors affecting HbA_{1c} levels. Changes in diabetes therapy or management may influence HbA_{1c} levels even in a short time frame. Glycation of hemoglobin reflects the weighted mean of preceding mean glucose over a considerably longer period of time.[15] For example, glucose levels during the most recent 4- to 6-week period will have a greater influence on the HbA_{1c} result compared to levels from the prior 6 weeks. Hence, if a patient experiences a recent change in acute glucose levels (ie, use of automated insulin delivery systems or sickness or glucocorticoid treatment), the HbA_{1c} will be disproportionately affected by the most recent glucose levels. Second, although point-of-care capillary HbA_{1c} measurement devices are useful in clinical care, they are limited by the accuracy and higher variability between instruments, and therefore, the use of point-of-care HbA_{1c} devices may be another factor in inducing HbA_{1c} measurement errors.[16] Third, erythrocyte turnover issues and shorter erythrocyte lifespan would underrepresent earlier glucose management.[1,2] Therefore, measured HbA_{1c} and eA_{1c} may not reflect the glycemic management of the same timeframe which may cause the discordance and unstable repeated measures.

The strength of this study is the longitudinal study design with data collection over 7 years with up to 15 clinic visits to evaluate the HbA_{1c}-eA_{1c} relationship. Moreover, we used 28 days of CGM data (compared to SMBG in previous studies) to estimate A_{1c} from sensor mean glucose. The small sample size, non-Hispanic white predominant study population, retrospective medical record-based data, and non-standardization of HbA_{1c} measurement with most measurements via point-of-care devices are limitations of this study.

Conclusions

In summary, we did not find an association between high HGI and incident DR over 7 years of follow-up. Most of the participants had alternating glycation status which highlights gaps in the glycation theory, and more research is needed to understand glycation of hemoglobin and its implication on diabetes complications.

Abbreviations

CGM, continuous glucose monitoring; eA_{1c}, A1c estimated; EMR, electronic medical record; HGI, hemoglobin glycation index; SD, standard deviation; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

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Declaration of Conflicting Interests

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