The Fast-Glycator Phenotype, Skin Advanced Glycation End Products, and Complication Burden Among People With Type 1 Diabetes

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OBJECTIVE

Existence of a fast-glycator phenotype among people with type 1 diabetes (T1D) is debated. Routine use of glucose sensors allows the comparison of long-term average glucose levels with laboratory HbA_{1c} values. We herein evaluated whether participants with T1D and HbA_{1c} values higher than their glucose management indicator (GMI) had greater accumulation of advanced glycation end products (AGEs) and chronic complications.

RESEARCH DESIGN AND METHODS

We included participants with T1D using the intermittently scanned continuous glucose monitoring system consecutively for at least 90 days and having a laboratory-determined HbA_{1c} at the end of observation. Skin AGEs were estimated using the skin autofluorescence (SAF) method. The complication burden was assessed by a standardized screening. The fast-glycator phenotype was defined as having a GMI to HbA_{1c} ratio <0.9.

RESULTS

We included 135 individuals with T1D (58% men; mean age, 44.4 years) with a mean diabetes duration of 21 years and a mean HbA_{1c} value of 7.7%. Thirty (22.2%) were defined as having the fast-glycator phenotype. As expected, fast glycators had higher HbA_{1c} (8.6% vs. 7.5%; $P < 0.001$) with similar 90-day mean glucose level (172 vs. 168 mg/dL; $P = 0.52$). Fast glycators had higher SAF than did other participants (2.5 vs. 2.1 arbitrary units; $P = 0.005$) and had a significantly higher prevalence of dyslipidemia (73% vs. 44%; $P = 0.005$), macroangiopathy (38% vs. 9%; $P = 0.001$), albuminuria (25% vs. 7%; $P = 0.038$), and retinopathy (61% vs. 38%; $P = 0.022$). After adjusting for age and dyslipidemia, the fast-glycator phenotype remained significantly associated with macroangiopathy (odds ratio 3.72; 95% CI 1.22–11.4).

CONCLUSIONS

In T1D, a fast-glycator phenotype defined by the GMI to HbA_{1c} ratio is characterized by elevated skin AGEs and is associated with the complication burden.

The formation of advanced glycation end products (AGEs) is a major determinant of diabetic complications (1). Glycation modifies the turnover of extracellular matrix

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proteins and affects the function of several cellular components, including enzymes, receptors, cytoskeletal proteins, and nucleic acids (2). HbA_{1c} is the prototypic AGE used for diagnosing diabetes and monitoring glycemic control. Given the strong direct correlation between HbA_{1c} and the risk of chronic complications, especially microvascular, measuring HbA_{1c} has been a mainstay of diabetes management for decades. Yet, there is substantial heterogeneity in glycation among individuals (3). Although glucose exposure is the primary driver of glycation, several other factors contribute to the glycation gap (4), including red blood cell permeability, oxidative stress, velocity of deglycation, protein turnover, and poorly identified genetic or epigenetic factors (5). Therefore, the relationship between mean glucose values and HbA_{1c} shows a substantial dispersion around the regression line and may not be linear over time (6). This variability has been confounded by the inaccurate estimation of glycemic exposure from self-monitoring of blood glucose (SMBG) or short periods (7–14 days) of interstitial continuous glucose monitoring (CGM). Therefore, it is still controversial whether a true "fast-glycator" phenotype exists—that is, a condition of excess glycation at means of glycemic exposure.

Recently, the widespread use of the intermittently scanned CGM (isCGM) system in routine care has opened the possibility of accurately estimating mean glucose in several patients consecutively over months or years (7). The glucose management indicator (GMI) has been derived from mean interstitial glucose levels to reflect the expected value of HbA_{1c} (8). This allows the unprecedented opportunity to compare the true glucose exposure with glycation indexes and to define fast glycators. Though GMI and laboratory HbA_{1c} values can differ substantially, due to factors other than the time being used for GMI calculation, anemia, and hemoglobinopathies, the variation in glycation rates remain poorly understood (9).

Skin AGEs have been reported to be associated with chronic complications and can be monitored noninvasively by measuring skin autofluorescence (SAF) (10). To our knowledge, no study has so far evaluated SAF in relation to HbA_{1c}, isCGM metrics, and chronic complications. In this study, we examined whether individuals with type 1 diabetes (T1D) and HbA_{1c} values higher than their GMI had greater accumulation of skin AGEs and chronic complications.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This was a retrospective observational study performed at a single center. According to local and national regulations on observational studies, the protocol was notified and cleared by the Ethical Committee of the Padua Province (prot. 31201). All patients provided written informed consent for the reuse of their electronic health data for research purposes.

Eligible patients were selected among those routinely attending the diabetes outpatient clinic of the University Hospital of Padova. Inclusion criteria were as follows: age $\geq$18 years; a diagnosis of T1D according to the American Diabetes Association criteria; therapy with multidose insulin or an insulin pump; disease duration of at least 1 year and being outside the honeymoon period; continuous use of the isCGM for at least 90 days before HbA_{1c} and SAF evaluation; and availability of an HbA_{1c} value at the end of the 90-day isCGM collection period and close to the SAF determination. Exclusion criteria were as follows: diagnosis of other forms of diabetes; lack of isCGM or HbA_{1c} data; lack of SAF measurement; concomitant diseases, conditions, or treatments that could affect HbA_{1c} (e.g., anemia) or glycemic control (e.g., acute infections, glucocorticoid therapy); and dark skin (11).

For all patients, we collected the following information: age, sex, disease duration, anthropometrics (height and body weight for the calculation of BMI), systolic and diastolic blood pressure as well as diagnosis of hypertension, lipid profile, Diabetes Control and Complications Trial (DCCT)–aligned HbA_{1c} measured by high-performance liquid chromatography, type and dose of insulin therapy, concomitant medications, and presence or absence of chronic complications.

Patients were divided into two groups: fast glycators and non–fast glycators (defined below). The primary objective was to detect a significant difference in skin AGEs between fast glycators and non–fast glycators. Secondarily, we examined the association between the fast-glycator phenotype and chronic complications.

Screening for Complications

At the outpatient diabetes clinic, all individuals with T1D are routinely subjected to a standardized protocol for screening for diabetic complications. Retinopathy was diagnosed on the basis of digital retinal photography and scored by an expert ophthalmologist according to the Early Treatment of Diabetic Retinopathy Study grading (12). Neuropathy was defined on the basis of cardiac autonomic tests (i.e., Valsalva maneuver, lying position to standing, deep breathing, and orthostatic hypotension), symptoms and signs of peripheral neuropathy, and the Michigan Neuropathy Screening Instrument questionnaire (13), eventually confirmed by nerve-conduction velocity. Chronic kidney disease was defined as the presence of micro- or macroalbuminuria (urinary albumin to creatinine ratio $>$30 mg/g) or a confirmed reduction of the estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration equation (14) to $<$60 mL/min/1.73 m^2. Cardiovascular disease was defined in the presence of a history of myocardial infarction, stroke, or transient ischemic attack; symptomatic peripheral arterial disease (e.g., claudication or rest pain); or revascularization of coronary, cerebral, or peripheral arteries. Macroangiopathy was defined as cardiovascular disease or asymptomatic evidence of macrovascular disease, including coronary stenosis $>$50%, carotid atherosclerotic plaques, or an ankle-brachial index $<$0.9.

Skin AGES

Accumulation of AGEs in the skin was evaluated by measuring SAF with the AGE Reader (Diagnoptics, Groningen, The Netherlands). The measure is performed with a noninvasive monitor applying ultraviolet light to excite autofluorescence in human skin tissue; SAF is derived from AGEs. The method has been extensively validated against the gold standard for measure of AGEs in skin biopsy samples (15). As recommended, readings were taken thrice for each patient at different points of the volar arm surface, and the average measurement was recorded.

Sensor Data

isCGM data were downloaded from a cloud portal (Libreview.com). We extracted all glucose readings automatically obtained by the sensor every 15 min, in addition to glucose values provided on demand when the patients scanned the sensor. From raw data, we recalculated the following metrics: average glucose level; GMI; time in range (TIR; 70–180 mg/dL), time below range (divided into time at <54 mg/dL and time at 54–69 mg/dL) and time above range (divided into time at 181–250 mg/dL and time at >250 mg/dL); and coefficient of variation (the percentage of SD over glucose mean). All these metrics were calculated for the entire observation period (90 days) or for the last 30 days and during daytime (6:00–24:00) and nighttime (00:01–05:59). GMI was calculated as 3.31 + 0.02392 × mean glucose (mg/dL).

Definition of Fast Glycators

Patients were defined as having a fast-glycator phenotype if their GMI derived from isCGM average glucose level during a 90-day period was higher than their laboratory HbA_{1c}, measured at the end of the 90-day period. We used the GMI to HbA_{1c} ratio and a cutoff <0.9 to define the fast-glycator phenotype. The threshold of 0.9 was chosen to separate two groups of participants with very similar mean glucose, but very different HbA_{1c}, values.

Statistical Analysis

Continuous data are presented as mean and SD, whereas categorical data are presented as percentages. Non-normal continuous variables were log-transformed before being analyzed with parametric tests. Two groups (fast glycators and non–fast glycators) were compared using the two-tailed Student *t* test for continuous variables or the χ^2 test for categorical variables. Linear correlations were assessed with the Pearson *r* coefficient. Multivariable linear regression was used to evaluate the association of the fast-glycator phenotype with end-point variables independently from confounders. Statistical significance was accepted at $P < 0.05$; SPSS, version 13.0, software was used.

RESULTS

Characteristics of Study Participants

We initially retrieved information on 186 individuals with T1D who had SAF and HbA_{1c} measured. Of these, 51 were excluded because of missing data to calculate GMI over the 90-day period from isCGM data. Characteristics of the remaining 135 participants included in the study are described in Table 1. More than half (58%) were men, the average age was 44.4 years, and the mean diabetes duration was 21 years. Most of the participants used a multidose insulin injection (92.6%; 7.4% used an insulin pump), and the average total daily insulin dose was 0.54 IU/kg; 6.7% of the 135 participants also received metformin. Glycemic control was suboptimal with HbA_{1c} of 7.7% (60 mmol/mol), mean isCGM glucose level of 168 mg/dL, and 57.6% of TIR. As for concomitant risk factors, 34.2% of participants had hypertension and 49% had dyslipidemia. Though renal function was mostly preserved (eGFR of 103 mL/min/1.73 m^2) and only two individuals (1.7%) had stage III chronic kidney disease, microangiopathy was prevalent: 48% of participants had neuropathy, 42.4% had retinopathy, and 11% had micro- or macroalbuminuria. Macroangiopathy was present in 14% of participants, but only 5.2% had a history of cardiovascular events.

Relationships Among GMI, Laboratory HbA_{1c}, and SAF

In the entire cohort, GMI and HbA_{1c} displayed a strong direct correlation ($r = 0.83$; $P < 0.0001$), but GMI was significantly lower than laboratory-determined HbA_{1c} values (7.4% vs. 7.7%; $P < 0.0001$). In a multiple linear regression model, both

Table 1—Clinical characteristics of study participants

Variable	All patients	Fast glycators	Non–fast glycators	*P* value
Patients, *n*	135	30	105	
Age, years	44 (14.1)	50.3 (14)	42.7 (13.7)	0.008
Male sex, %	58	42	58	0.362
Diabetes duration, years	21 (12.4)	23.5 (13.8)	20 (12)	0.22
Diabetes control				
HbA_{1c}, %	7.7 (1.1)	8.6 (1.2)	7.5 (0.9)	0.0001
Mean glucose, mg/dL	168 (31.9)	172 (32)	168 (31)	0.524
Coefficient of variation, %	36.5 (7.3)	39 (9.5)	36.7 (6.2)	0.214
TIR (70–180 mg/dL), %	56.3 (17.5)	54.1 (16)	57 (17)	0.270
Time below range (55–70 mg/dL), %	3.1 (2.5)	3.6 (2.7)	3.2 (2.3)	0.373
Time below range (≤54 mg/dL), %	1.2 (2.6)	1.9 (3.3)	0.97 (1.4)	0.141
Time above range (181–250 mg/dL), %	25.9 (9.3)	25.7 (9)	25.4 (8)	0.856
Time above range (>250 mg/dL), %	13.4 (13.9)	14.6 (11.7)	12.5 (12.9)	0.417
Risk factors				
BMI, kg/m^2	25.1 (3.6)	25 (3.4)	25 (3.7)	0.188
Hypertension, %	34.2	53	47	0.561
Systolic blood pressure, mmHg	136 (16.4)	136 (18)	136 (16)	0.93
Diastolic blood pressure, mmHg	79 (10.2)	79.9 (10.2)	79.2 (10)	0.11
Dyslipidemia, %	49	73	44	0.005
Total cholesterol, mg/dL	174 (27.3)	171 (27)	175 (27)	0.47
HDL cholesterol, mg/dL	62.5 (14.9)	61.2 (14.9)	63 (15)	0.572
LDL cholesterol, mg/dL	95.6 (25.1)	95 (22.6)	96 (26)	0.77
Triglycerides, mg/dL	78 (39.7)	78 (42)	79 (28)	0.91
Complications				
Cardiovascular disease, %	5.2	17	1.7	0.001
Macroangiopathy, %	14	38	9	0.001
eGFR, mL/min/1.73 m^2	103 (17.8)	99 (20)	104 (17)	0.21
Chronic kidney disease, %	1.7	5.7	3.2	0.385
Micro- or macroalbuminuria, %	11	25	7	0.038
Retinopathy, %	42.4	61	38	0.022
Neuropathy, %	48	48.3	41.8	0.538
Therapies				
Total insulin dose, IU/kg	0.54 (0.17)	0.5 (0.2)	0.5 (0.2)	0.9
Metformin, %	6.7	6.7	6.7	0.681
ACE inhibitors or ARB, %	27	36	23	0.163
Statins, %	42	60	37	0.022

Data are presented as mean (SD) unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

SAF (β = 0.14; P = 0.05) and GMI (β = 0.64; $P < 0.001$) values were significantly associated with laboratory-determined HbA_{1c}. The independent association between SAF and HbA_{1c} at means of GMI was reduced and no longer significant after adjusting for age (β = 0.08; P = 0.194). Thirty participants (22.2%) had a GMI value that was <0.9 times their laboratory HbA_{1c} and these participants were defined as having the fast-glycator phenotype (Fig. 1*A*).

Characteristics of Fast Glycators

The 30 fast glycators were compared with the remaining 105 patients. Fast glycators had strikingly higher laboratory-determined HbA_{1c} values (mean values, 8.6% vs. 7.5%, respectively; $P < 0.0001$; equal to ∼1 SD difference) with similar mean interstitial glucose levels (172 vs. 168 mg/dL, respectively; P = 0.52). When we analyzed HbA_{1c} values collected in the preceding 6 months, this between-group difference was confirmed (8.5% vs. 7.5%, respectively; $P < 0.0001$), suggesting that the fast-glycator phenotype is stable over at least 6 months.

As compared with non–fast glycators (Table 1), fast glycators were significantly older, had a higher prevalence of dyslipidemia, and more often received statins. They also had higher prevalence of cardiovascular disease (10-fold), macroangiopathy (4.2-fold), albuminuria (3.6-fold), and retinopathy (1.6-fold) (Fig. 1*B*). In addition, fast glycators had increased SAF levels (2.5 vs. 2.1 arbitrary units; P = 0.005), confirming the excess glycation (Fig. 1*C*). Use of metformin was not associated with SAF or proportion of fast glycators.

All glucose metrics calculated from isCGM were similar between the two groups (Fig. 1*D*), including the coefficient of variation (Table 1). There was a minor trend toward less TIR and more time in hypo- and hyperglycemia among fast glycators, though the differences were far from reaching statistical significance. When the time for calculating isCGM-derived mean glucose values was restricted to the last 30 days, the proportion of fast glycators, and the differences in SAF, HbA_{1c}, and complication burden did not change, despite there still being no differences in isCGM metrics (data not shown).

Features Independently Associated With the Fast-Glycator Phenotype

The association between the fast-glycator phenotype and increased SAF was no longer significant after adjustment for age (Table 2). When adjusted for age, the association with retinopathy (P = 0.31) and albuminuria (P = 0.091) also lost statistical significance. The association between fast glycators and macroangiopathy remained statistically significant, however, when adjusted for age and dyslipidemia, with an odds ratio of 3.73 (95% CI 1.22–11.4; P = 0.021). Further adjustment for the time spent in each glucose range did not modify the result (odds ratio 3.60).

CONCLUSIONS

In this study, 22.2% of individuals with T1D in our cohort were identified as fast glycators who had an average HbA_{1c} 1.1% higher than their 90-day GMI. We report that fast glycators had higher glycation in the skin, as determined by SAF, and a heavier burden of chronic complications. Notably, fast glycators were significantly older than other patients, and part of the clinical phenotype associated

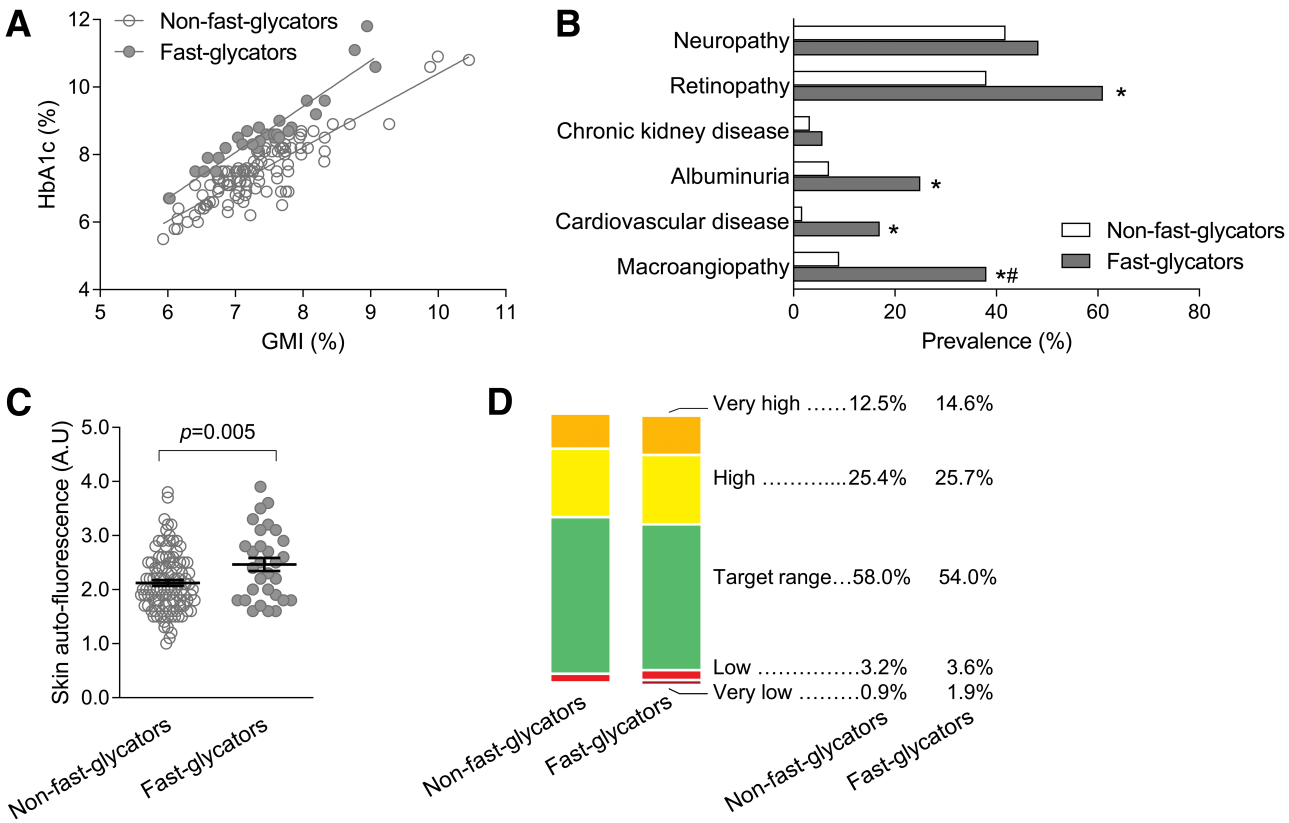

Figure 1—Clinical features of the fast-glycator phenotype. *A*: The correlation plot between GMI and laboratory HbA_{1c} shows that fast glycators have a higher HbA_{1c} for any sensor mean glucose-derived GMI than do non–fast glycators. *B*: Prevalence of chronic complications in fast glycators and non–fast glycators (*unadjusted $P < 0.05$; #adjusted $P < 0.05$). *C*: SAF levels in fast glycators and non–fast glycators. *D*: Ambulatory glucose profile of the two groups of patients. a.u., arbitrary units.

Table 2—Adjusted associations among the fast-glycator phenotype, SAF, and complications

	Dependent variable (β; *P* value)			
Independent variable	SAF	Albuminuria	Retinopathy	Macroangiopathy
Fast-glycator phenotype	0.01; 0.14	−1.03; 0.093	0.50; 0.31	1.32; 0.021
Age	0.63; <0.001	−0.02; 0.36	0.06; <0.001	0.06; 0.035
Dyslipidemia	N/A	N/A	N/A	2.21; 0.044

The dependent variable SAF was entered in a linear regression, whereas the other dependent variables (complications) were entered in logistic regressions. When the association between fast glycators and the dependent variable remained significant after adjusting for age, it was also adjusted for the presence of dyslipidemia. N/A, not assessed.

with fast glycators was likely due to aging (6). Indeed, concentrations of tissue AGEs are known to increase with age, and SAF is directly correlated to chronological age (2,16), which is traditionally attributed to the progressive accumulation and the slow removal of tissue AGEs. Yet, HbA_{1c} does not accumulate indefinitely, because red blood cells are continuously renewed. Therefore, aging would not only allow the accumulation of slowly removable tissue AGEs but also enhance the glycation process, possibly through an age-dependent reduction in antioxidant capacity (17). Yet, hemoglobin within red blood cells is likely to have a different glycation kinetic as compared with collagen in the skin and with other tissue proteins involved in chronic complications. Therefore, different determinants of glycation may apply to different tissues.

The existence of a discrepancy between measures of glucose exposure (mean glucose or GMI) and laboratory HbA_{1c} has been known for decades, but a clear explanation is not available. At least part of such variability in the correlation between expected and observed HbA_{1c} is due to the uncertainty in the estimation of glucose exposure. Initial studies, like the DCCT, calculated mean glucose from spot SMBG (18,19), which is intrinsically unable to capture the entire spectrum of glycemic excursions and exposure. With the advent of CGM, several studies calculated mean glucose from short periods of interstitial glucose monitoring, typically 7 to 14 days (20). When comparing mean glucose during 7–14 days with HbA_{1c}, this approach is also prone to bias, because HbA_{1c} reflects the mean glycemic exposure of 2 to 3 months, though not linearly. It is therefore likely that longer periods of interstitial glucose monitoring are needed to accurately capture the glycemic exposure determining HbA_{1c} values (9). This is now possible, thanks to the widespread availability of isCGM. Even this approach is not free from bias, however, because interstitial glucose could systematically underestimate or overestimate blood glucose levels in some patients (21).

Our findings are consistent with the existence of a true fast-glycator phenotype. Patients identified as fast glycators had similar isCGM-derived glucose metrics as non–fast glycators and had not only higher HbA_{1c} values but also elevated SAF, consistent with an enhanced glycation capacity. Because glycation is a determinant of tissue damage in diabetes, the observation that fast glycators also had strikingly higher (up to 10-fold) prevalence of chronic complications strongly supports the clinical relevance of a fast-glycator phenotype. When adjusted for age, the associations of fast glycators with SAF and with microangiopathy were no longer significant. This finding suggests that at least part of the fast-glycator phenotype is explained by aging and implies that aging of people with T1D can accelerate the onset of microvascular damage. After adjusting for age, a trend association of the fast-glycator phenotype with albuminuria was still evident, whereas that with retinopathy was not. This is in line with the notion that diabetes duration affects the risk of retinopathy more than the risk of nephropathy (22). At the same time, we found that the association between fast glycators and macroangiopathy remained significant after adjusting for age and dyslipidemia (the other relevant, imbalanced covariate) and could not be explained by differences in isCGM metrics. Therefore, the impact of excess glycation on macrovascular complications seems to project beyond the acceleration imparted by aging. This observation is consistent with the notion that SAF can also be considered a marker of cardiovascular risk beyond age and other traditional risk factors (16). In the Pittsburgh Epidemiology of Diabetes Complications Study, each 1% increase in HbA_{1c} was associated with a 13–26% higher relative risk of cardiovascular disease in people with T1D (23), suggesting that the 4.2-fold higher proportion of patients with macroangiopathy among fast glycators should be attributed not only to the HbA_{1c} difference but also to excess long-term accumulation of tissue AGEs.

In our study, the prevalence of fast glycators, characterized by a 1.1% higher HbA_{1c} compared with GMI, was close to the proportion of patients who had a difference of ≥1% between laboratory-determined HbA_{1c} and GMI calculated from <30-day CGM data (24). Here, we identified fast glycators on the basis of the ratio between 90-day isCGM-derived GMI and laboratory HbA_{1c} values. Previously, a hemoglobin glycation index (HGI) was proposed as the difference between HbA_{1c} estimated from fasting plasma glucose level and laboratory-determined HbA_{1c} (25). Our approach can be considered more reliable because *1*) we used long-term glucose monitoring data to estimate GMI; and *2*) the ratio of GMI to HbA_{1c} provides a more balanced representation of the discordance between expected and observed HbA_{1c} as compared with the difference. In fact, with regard to the latter point, a 1.0% difference in HbA_{1c} is much more clinically relevant at 7% HbA_{1c} (e.g., 7.5% vs. 6.5%) than at 10% (10.5% vs. 9.5%). In a cohort of 110 children with T1D, HGI was correlated with SAF (26). However, in the DCCT, the HGI was not predictive of subsequent complications independently from HbA_{1c}, whereas the effect of HGI on complication risk was mostly explained by its linear association with HbA_{1c} (18,19). Here, we are not proposing a new index of glycation gap, rather we show that a discrepancy between mean glucose level and HbA_{1c} is linked to a distinctive clinical phenotype in terms of tissue glycation and complication burden.

Our study has key limitations. First, the sample size was relatively small, and the study may be underpowered for some of the subanalyses. For example,

in a larger cohort and with greater statistical power, the age-independent associations among fast glycators, SAF, and microangiopathy (especially albuminuria) may be significant. Second, all patients were Caucasian and were enrolled at a single center, with no external validation in an independent cohort, thereby limiting generalizability of the findings. This selection, at least in part, was due to the exclusion of people with dark skin, for whom SAF determination is unreliable (11). Third, at present, we have no longitudinal follow-up and we cannot evaluate whether fast glycators have a risk of new-onset or worsening complications. Finally, we cannot rule out that part of the difference in HbA_{1c} values between fast glycators and non–fast glycators was due to glucose underestimation by the isCGM. Yet, if this phenomenon were not intrinsically due to glycation, we would not see differences in SAF and complications between the two groups.

Our study has notable strengths. First, we captured glucose exposure from long-term interstitial glucose monitoring, which is far more accurate than the estimation of HbA_{1c} from fasting glucose, SMBG, or short-term CGM. Second, we confirmed that the fast-glycator phenotype defined by the GMI to HbA_{1c} ratio is characterized by excess glycation in the skin, as revealed by SAF, providing a new biological validation that is further supported by the greater prevalence of complications.

In conclusion, our new data support the view that patients with laboratory-determined HbA_{1c} higher than GMI have excess glycation and may be at higher risk of developing complications, especially macrovascular. This hypothesis needs to be confirmed in longitudinal studies.

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References

1. Ahmed N. Advanced glycation endproducts–role in pathology of diabetic complications. Diabetes Res Clin Pract 2005;67:3–21
2. Chaudhuri J, Bains Y, Guha S, et al. The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. Cell Metab 2018;28:337–352
3. Chalew SA, McCarter RJ, Thomas J, Thomson JL, Hempe JM. A comparison of the glycosylation gap and hemoglobin glycation index in patients with diabetes. J Diabetes Complications 2005;19:218–222
4. Nayak AU, Singh BM, Dunmore SJ. Potential clinical error arising from use of HbA1c in diabetes: effects of the glycation gap. Endocr Rev 2019;40:988–999
5. Leslie RD, Cohen RM. Biologic variability in plasma glucose, hemoglobin A1c, and advanced glycation end products associated with diabetes complications. J Diabetes Sci Technol 2009;3:635–643
6. Xu Y, Dunn TC, Ajjan RA. A kinetic model for glucose levels and hemoglobin A1c provides a novel tool for individualized diabetes management. J Diabetes Sci Technol 2021;15:294–302
7. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. Diabetes Care 2020;43:2153–2160
8. Bergenstal RM, Beck RW, Close KL, et al. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care 2018;41:2275–2280
9. Gomez-Peralta F, Choudhary P, Cosson E, Irace C, Rami-Merhar B, Seibold A. Understanding the clinical implications of differences between glucose management indicator and glycated haemoglobin. Diabetes Obes Metab 2022;24:599–608
10. Bos DC, de Ranitz-Greven WL, de Valk HW. Advanced glycation end products, measured as skin autofluorescence and diabetes complications: a systematic review. Diabetes Technol Ther 2011;13:773–779
11. Atzeni IM, Boersema J, Pas HH, et al. Is skin autofluorescence (SAF) representative of dermal advanced glycation endproducts (AGEs) in dark skin? A pilot study. Heliyon 2020;6:e05364
12. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98(5 Suppl.):786–806
13. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994;17:1281–1289
14. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
15. Mulder DJ, Water TV, Lutgers HL, et al. Skin autofluorescence, a novel marker for glycemic and oxidative stress-derived advanced glycation endproducts: an overview of current clinical studies, evidence, and limitations. Diabetes Technol Ther 2006;8:523–535
16. Koetsier M, Lutgers HL, de Jonge C, Links TP, Smit AJ, Graaff R. Reference values of skin autofluorescence. Diabetes Technol Ther 2010;12:399–403
17. Kim JW, No JK, Ikeno Y, et al. Age-related changes in redox status of rat serum. Arch Gerontol Geriatr 2002;34:9–17
18. Lachin JM, Genuth S, Nathan DM, Rutledge BN. The hemoglobin glycation index is not an independent predictor of the risk of microvascular complications in the Diabetes Control and Complications Trial. Diabetes 2007;56:1913–1921
19. McCarter RJ, Hempe JM, Gomez R, Chalew SA. Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. Diabetes Care 2004;27:1259–1264
20. Joung HN, Kwon HS, Baek KH, Song KH, Kim MK. Consistency of the glycation gap with the hemoglobin glycation index derived from a continuous glucose monitoring system. Endocrinol Metab (Seoul) 2020;35:377–383
21. Moser O, Sternad C, Eckstein ML, et al. Performance of intermittently scanned continuous glucose monitoring systems in people with type 1 diabetes: a pooled analysis. Diabetes Obes Metab 2022;24:522–529
22. Bebu I, Braffett BH, Schade D, et al.; DCCT/EDIC Research Group. An observational study of the equivalence of age and duration of diabetes to glycemic control relative to the risk of complications in the combined cohorts of the DCCT/EDIC Study. Diabetes Care 2020;43:2478–2484
23. Miller RG, Anderson SJ, Costacou T, Sekikawa A, Orchard TJ. Hemoglobin A1c level and cardiovascular disease incidence in persons with type 1 diabetes: an application of joint modeling of longitudinal and time-to-event data in the Pittsburgh Epidemiology of Diabetes Complications Study. Am J Epidemiol 2018;187:1520–1529
24. Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA1c and glucose management indicator discordance: a real-world analysis. Diabetes Technol Ther 2021;23:253–258
25. Hsia DS, Rasouli N, Pittas AG, et al.; D2d Research Group. Implications of the hemoglobin glycation index on the diagnosis of prediabetes and diabetes. J Clin Endocrinol Metab 2020;105:e130-8
26. Felipe DL, Hempe JM, Liu S, et al. Skin intrinsic fluorescence is associated with hemoglobin A(1c) and hemoglobin glycation index but not mean blood glucose in children with type 1 diabetes. Diabetes Care 2011;34:1816–1820