

ORIGINAL ARTICLE

Interindividual variability in average glucose-glycated haemoglobin relationship in type 1 diabetes and implications for clinical practice

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Abstract

Aim: Glycated haemoglobin (HbA1c) can fail to reflect average glucose levels, potentially compromising management decisions. We analysed variability in the relationship between mean glucose and HbA1c in individuals with diabetes.

Materials and Methods: Three months of continuous glucose monitoring and HbA1c data were obtained from 216 individuals with type 1 diabetes. Universal red blood cell glucose transporter-1 Michaelis constant K_M and individualized apparent glycation ratio (AGR) were calculated and compared across age, racial and gender groups.

Results: The mean age (range) was 30 years (8-72) with 94 younger than 19 years, 78 between 19 and 50 years, and 44 were >50 years. The group contained 120 women and 96 men with 106 white and 110 black individuals. The determined K_M value was 464 mg/dl and AGR was (mean \pm SD) 72.1 ± 7 ml/g. AGR, which correlated with red blood cell lifespan marker, was highest in those aged >50 years at 75.4 ± 6.9 ml/g, decreasing to 73.2 ± 7.8 ml/g in 19-50 years, with a further drop to 71.0 ± 5.8 ml/g in the youngest group ($p < 0.05$). AGR differed between white and black groups (69.9 ± 5.8 and 74.2 ± 7.1 ml/g, respectively; $p < .001$). In contrast, AGR values were similar in men and women (71.5 ± 7.5 and 72.5 ± 6.6 ml/g, respectively; $p = .27$). Interestingly, interindividual AGR variation within each group was at least four-fold higher than average for between-group variation.

Conclusions: In this type 1 diabetes cohort, ethnicity and age, but not gender, alter the HbA1c-glucose relationship with even larger interindividual variations found within each group than between groups. Clinical application of personalized HbA1c-glucose relationships has the potential to optimize glycaemic care in the population with diabetes.

KEYWORDS

age differences, apparent glycation ratio, gender differences, glucose-HbA1c relationship, kinetic modelling, racial differences, RBC lifespan

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1 | INTRODUCTION

It is well accepted that good glycaemic control in diabetes reduces the risk of microvascular complications and long-term macrovascular disease.¹⁻⁵ While glycated haemoglobin (HbA1c) has been a key clinical measure to aid in the management of patients with diabetes, this glycaemic measure is not without limitations. HbA1c is a good marker of the risk of complications at a population level but there are differences between individuals that may lead to inappropriate management decisions.⁶ Previous work has shown that haemoglobin glycation can vary between individuals for the same average glucose levels, thus under- or overestimating the risk of complications, or even resulting in the misdiagnosis of diabetes.⁷⁻¹⁰ This gave rise to the concept of glycation gap, representing the difference between predicted and actual HbA1c.¹¹ Importantly, the glycation gap has shown associations with the risk of diabetes complications and adverse outcome, moving this from a biochemical concept into a clinical risk marker.¹²⁻¹⁶

Reports of racial differences in haemoglobin glycation have been steadily emerging for the past two decades^{8,17-20} but studies have generally relied on small patient populations and/or used limited glucose data, thus failing to provide concrete advice on how to address this clinical issue. A more recent comprehensive study using HbA1c, blood glucose and continuous glucose monitoring (CGM) data showed that HbA1c overestimates average glucose control in non-Hispanic black individuals by 0.4 percentage points of HbA1c compared with non-Hispanic white individuals.²⁰ The authors concluded that interpretation of HbA1c for each person requires a better understanding of the relationship with average glucose at an individual level. Of note, in the study,²⁰ no racial disparity in albumin or fructosamine glycation was found, indicating that the observed differences are HbA1c-specific. In another study, it was also found that the racial disparity in HbA1c persists after statistical adjustment for fructosamine levels.²¹ The variable nature of the glucose-HbA1c relationship suggests that the observed changes are probably related to individually altered uptake of glucose by red blood cells (RBC) and RBC lifespan, as haemoglobin glycation occurs inside the RBC. Taken together, there is a clear clinical need to understand the reasons for the differences in the relationship between HbA1c and average glucose levels across individuals. This, in turn, will enable the development of reliable personal glycaemic measures that more accurately reflect tissue glucose exposure in organs prone to diabetes complications.

A recent glucose-HbA1c kinetic model has been described accounting for individual RBC glucose uptake and cellular lifespan,²²⁻²⁵ which can be represented by an individual-specific apparent glycation ratio (AGR). In this model, AGR dictates the individual relationship between HbA1c and average glucose. The aim of the current work was to study the effects of age, race and gender on AGR to understand the role of these unmodifiable factors on the relationship between HbA1c and average glucose levels. Secondary aims included associating the AGR with RBC indices, which can reflect the RBC lifespan, by comparing their changes among age, race and gender groups. Understanding AGR variability will help to personalize HbA1c targets, thus providing optimal glycaemic control for each individual

thus minimizing the risks of both hyper- and hypoglycaemic complications.

2 | MATERIALS AND METHODS

2.1 | Derivation of the relationship among average glucose, glycated haemoglobin and apparent glycation ratio

In our previous work,²² following the steady state, HbA1c and glucose relationship were derived using the equation: $EA = g / (K^{-1} + g)$ and $g = (K_M \times [G]) / (K_M + [G])$, where K is the AGR; EA and $[G]$ are steady state for HbA1c and glucose, respectively; K_M is the Michaelis constant for glucose-glucose transporter-1 (glucose-GLUT1). When we approximate steady-state glucose and HbA1c with average glucose (AG) and HbA1c, we derive Equation (1) (more details in Appendix S1), and therefore the individual relationship between average glucose and HbA1c can be determined by an AGR value as follows:

$$AGR = \frac{AG^{-1} + K_M^{-1}}{HbA1c^{-1} - 1} \quad (1)$$

2.2 | Data acquisition

CGM and central laboratory HbA1c measurements were obtained using publicly available data from a previous study on the racial difference in the relationship of mean glucose and HbA1c for people with type 1 diabetes (T1D).²⁰ The number of non-Hispanic black and non-Hispanic white individuals with T1D recruited was largely similar. Professional CGM data were collected using Abbott Diabetes Care's Freestyle Libre Pro Flash Glucose Monitoring system together with up to six central lab HbA1c measurements using non-porous ion-exchange high-performance chromatography (G8 HPLC Analyzer, Tosoh Biosciences Inc.). RBC indices were also collected including red cell distribution width (RDW). This analysis included 216 individuals with both CGM and HbA1c data available. Individuals had a median (range) of 6082 (109-8900) CGM readings and five (two to six) HbA1c readings.

2.3 | Average glucose-glycated haemoglobin relationship and individual apparent glycation ratio calculation

Laboratory HbA1c is modulated by average glucose levels, red cell lifespan and cellular glucose uptake, the latter being mediated by GLUT1. As a reference, the expected population value for AGR is 65.1 ml/g, based on a mean RBC lifespan of 105 days²⁶ and RBC glucose uptake of 0.62 ml/g/day.²⁷ AG (mg/dl) is the average glucose, HbA1c (National Glycohemoglobin Standardization Program %) is the average HbA1c, and K_M (mg/dl) is the Michaelis constant of glucose and GLUT1 on RBC membranes, which is assumed to be a universal

parameter. With K_M universally constant, average glucose, average HbA1c and AGR values were calculated for all individuals using Equation (1). The effects of race, gender and age on AGR values were then analysed, and further association with RDW, which can reflect RBC lifespan,^{28,29} evaluated.

2.4 | Analyses by race, gender and age

For the purpose of this work, patient groups were divided according to race into non-Hispanic black African American and non-Hispanic white individuals. Further separate analyses by gender and age were conducted. The analysis of age was performed by tertiles within the group, and secondarily by three clinically relevant groups of: (a) young (age ≤ 18 years); (b) adult (age 18-50 years); and (c) older adult (>50 years).

2.5 | Associations between apparent glycation ratio and red blood cell indices

As AGR is the ratio of apparent haemoglobin glycation rate and RBC turnover rate, AGR values may be associated with biomarkers that reflect RBC turnover rate or lifespan (RBC lifespan = $1/\text{RBC turnover}$). We therefore investigated the relationship of RDW to AGR values across the groups. The group average RDW should follow the same trend as AGR, assuming similar within-group distribution of apparent haemoglobin glycation rate.

2.6 | Statistical analysis and power calculations

Mean glucose concentration of each individual was calculated from the average of all available glucose concentrations. Similarly, average HbA1c was calculated from all available central lab HbA1c values (point-of-care HbA1c values were excluded from analysis). Primary analysis used a Deming regression for best fit AGR in a group of subjects. Deming regression (detailed in the Appendix S1) was used to minimize deviations on both average glucose and HbA1c. The K_M value was set to a universal value (464 mg/dl; see Appendix S1) and the between-group comparisons were done on group average AGR values.

Based on an expected AGR of 70 ml/g in this dataset and an overall SD = 7 ml/g, a sample size of 86 per group is required to detect a difference of 3 ml/g (about 5% of the expected AGR) with a power of 80% and significance level of 0.05. Our dataset included 216 individuals with over 100 individuals in each of the two main racial groups. Between-group analyses were conducted using one-way ANOVA and unpaired two-sample t-test in Python/Scipy,³⁰ with significance level of $p < .05$ for comparisons. We calculated the within-group variances as the square of the corresponding SDs. In addition, the between-group variances were calculated from the square of the corresponding group averages.

TABLE 1 Main characteristics of study individuals

Count or mean \pm SD (range)	All	Black	White	Male	Female	Young (≤ 18)	Adult (19-50)	Older adult (>50)
Subject count	216	110	106	96	120	90	82	44
Age (years)	30.5 \pm 17.9 (8.5-72.3)	31.5 \pm 17.0 (8.5-71.1)	29.4 \pm 18.7 (9.4-72.3)	29.3 \pm 19.1 (8.5-72.3)	31.4 \pm 16.8 (8.6-68.2)	13.7 \pm 2.5 (8.5-17.7)	34.0 \pm 9.1 (18.2-49.9)	57.9 \pm 6.6 (50.3-72.3)
RDW (%)	13.3 \pm 1.2 (7.8-20)	13.6 \pm 1.2 (11.6-20)	12.9 \pm 1.1 (7.8-19.3)	13.2 \pm 1.2 (7.8-19.3)	13.3 \pm 1.3 (11.3-20)	p-value: N/A	13.4 \pm 1.3 (11.8-20)	13.5 \pm 0.9 (11.6-15.6)
Average HbA1c	8.6 \pm 1.4 (6.1-12.1)	9.0 \pm 1.4 (6.1-12.1)	8.2 \pm 1.2 (6.1-11.4)	8.6 \pm 1.3 (6.1-11.8)	8.7 \pm 1.5 (6.1-12.1)	p-value = 0.04	8.3 \pm 1.3 (6.1-12.1)	8.2 \pm 1.1 (6.1-11.4)
NGSP (%)	187 \pm 47 (107-333)	193 \pm 49 (107-331)	181 \pm 45 (108-333)	186 \pm 47 (113-333)	187 \pm 48 (107-326)	p-value < 0.001	174 \pm 43 (107-278)	162 \pm 30 (108-248)
Average glucose (mg/dl)						p-value = 0.06		

Note: Within group ANOVA p-values are listed. In all pairwise comparisons among age groups with t-test, the younger group is significantly different to other two age groups with $p < .05$, while the adult and older adult age groups are not significant different to each other with $p > .05$.

p-values < 0.05 are in bold.

Abbreviations: HbA1c, glycated haemoglobin; NGSP, National Glycohemoglobin Standardization Program; RDW, red cell distribution width.

3 | RESULTS

3.1 | Subject distribution

Good quality CGM and HbA1c data were available for all 216 individuals with T1D, which included 96 males and 120 females. CGM readings had a median (range) of 6082 (109-8900), while median HbA1c readings were five (two to six). In total, 110 were non-Hispanic American African and 106 were non-Hispanic white individuals. The

tertile age groups had 72 subjects in each group with mean age of 12.9 (range 8.5--16), 25.8 (range 16--38) and 52.6 (range 38--72.3) years. By clinically relevant age groups, there were 90, 82 and 44 individuals in the young (≤ 18), adult (18--50) and older adult (>50) age groups, with mean \pm SD ages of 13.7 ± 2.5 , 34.0 ± 9.1 and 57.9 ± 6.6 years, respectively (Table 1). Each person had 5826 ± 1728 glucose readings and 4.8 ± 0.7 laboratory HbA1c readings, collected over 85 ± 15.5 days. The RDW distribution is also included in Table 1 as a rough indicator of RBC lifespan in our analysis.

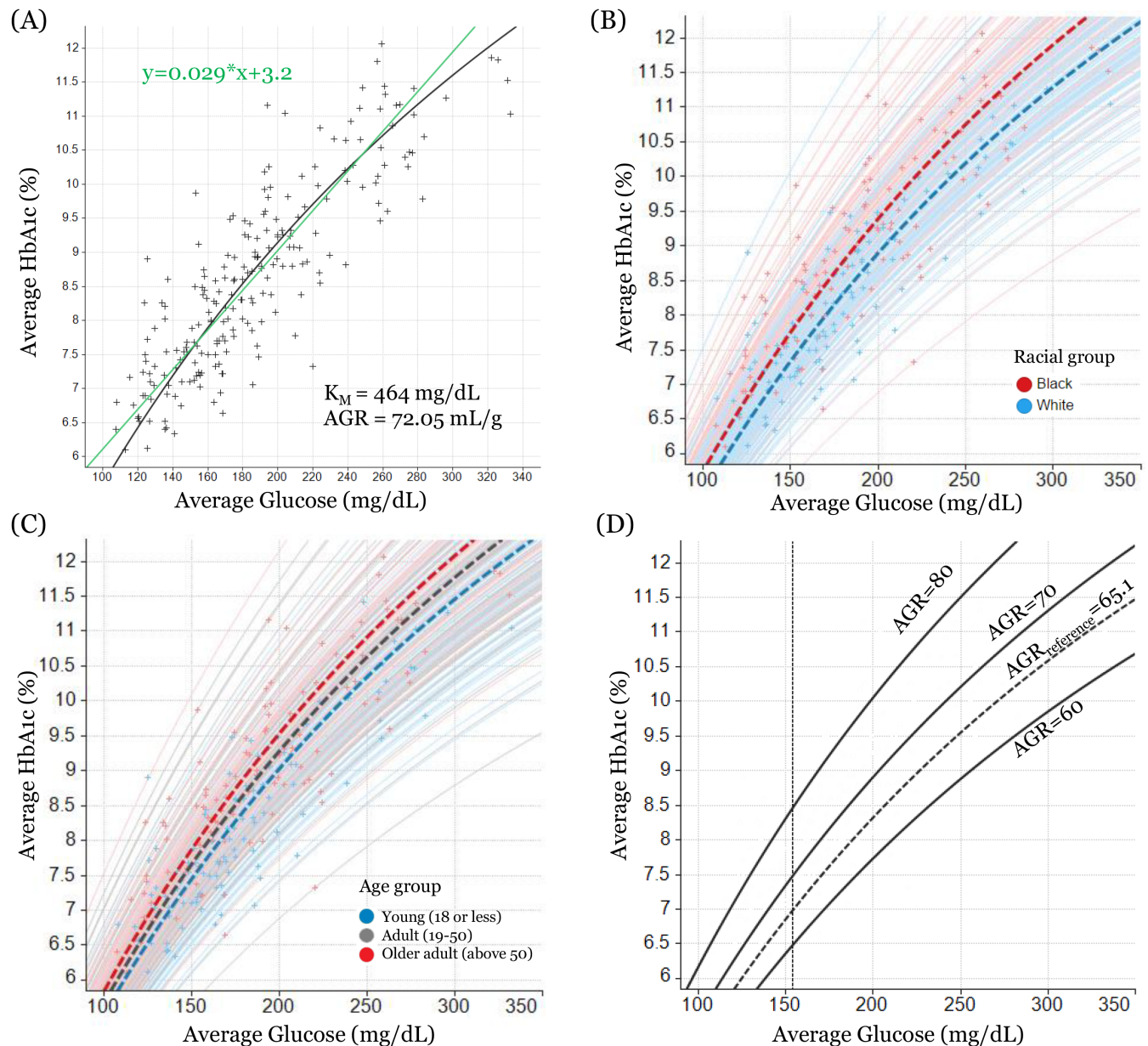


FIGURE 1 A, Regression lines: linear function (green) and Equation (1) (black) were used in the full cohort studied. B, Individual (solid lines) and group average (dashed lines) steady-state glucose-A1c curves, plotted in blue and red for white and black racial groups, respectively. C, Individual (solid lines) and group average (dashed lines) steady-state glucose-A1c curves, plotted in blue, grey and red for young (≤ 18), adult (19-50) and old (>50) age groups, respectively. D, Steady-state glucose and HbA1c relationship under different AGR values. Reference AGR based on reported red blood cell glucose uptake and lifespan in people without diabetes is plotted as a dotted line. Outer solid lines (AGR = 60.0 and 80.0) spans more than 90% of individuals in this dataset. AGR, apparent glycation ratio; HbA1c, glycated haemoglobin

3.2 | Apparent glycation ratio estimation for all individuals

The relationship between HbA1c and average glucose was evaluated using a total least squares method by a linear and a curvilinear regression based on Equation (1) (Figure 1A). The estimated K_M and cohort AGR were 464 mg/dl and 72.1 ± 7.0 ml/g, respectively. The K_M value is close to the literature reported value of 472 mg/dl.³¹ Therefore, K_M of 464 mg/dl was used as a universal constant throughout. Importantly, our model shows that the relationship between average glucose and HbA1c is non-linear (Appendix S1, Figure S1).

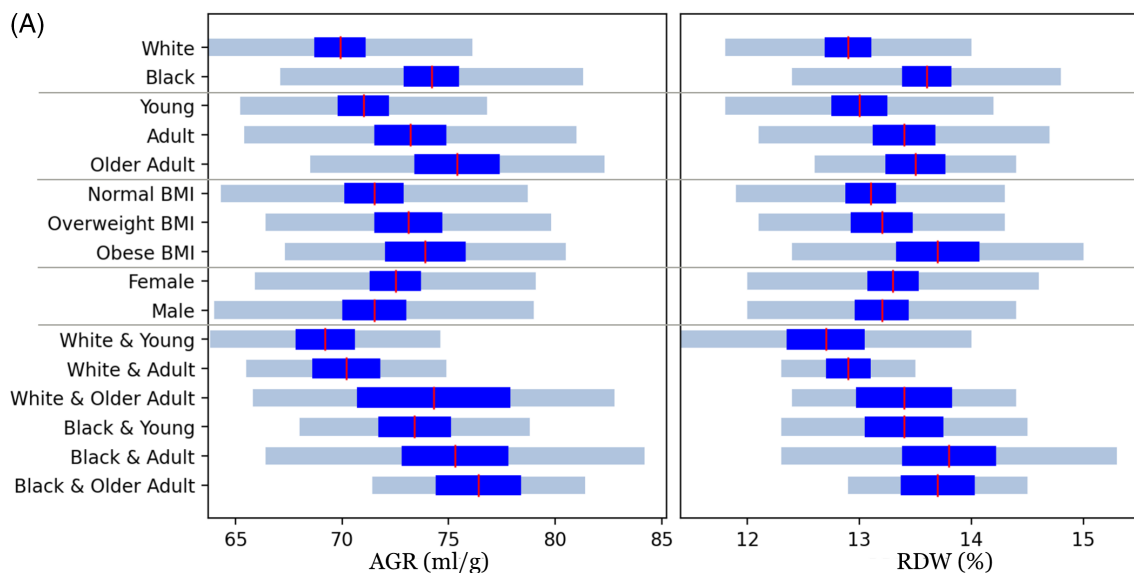
3.3 | Individual distribution of apparent glycation ratio

Individual AGR curves plotted show a wide range of glycation tendencies, including divergence between the two racial groups (Figure 1B) and age groups (Figure 1C). Representative AGR curves were plotted, which

includes a reference curve having an AGR value of 65.1 ml/g, calculated from reference RBC lifespan and glucose uptake for individuals without diabetes (Figure 1D). Compared with reference AGR of 65.1 ml/g, individuals with T1D in this dataset had a higher glycation tendency, shown by the higher average AGR value of 72.1 ml/g. In general, 5 units of AGR increase results in HbA1c increase of approximately 0.5% (approximately 5 mmol/mol) at a mean glucose of 154 mg/dl (8.6 mmol/L). Therefore, compared with the reference AGR of 65.1 ml/g having an HbA1c at 7.0% is associated with a mean glucose of 154 mg/dl but another person with an AGR of 80 ml/g would be expected to have an HbA1c of 8.5% at mean glucose 154 mg/dl. Higher mean glucose corresponds to larger changes in HbA1c for the same difference in AGR.

3.4 | Effects of race, age, gender and body mass index on apparent glycation ratio values

Our data show that AGR is modulated by race with mean \pm SD AGR values of 74.2 ± 7.1 and 69.9 ± 6.2 ml/g for the black and white groups,



(B)

	Group	N	AGR (ml/g)		RDW (%)	
			Average(SD)	ANOVA p-value	Average(SD)	ANOVA p-value
Race	Black	110	74.2 (7.1)	<0.001	13.6 (1.2)	<0.001
	White	106	69.9 (6.2)		12.9 (1.1)	
Age	Young ≤ 18	90	71.0 (5.8)	0.002	13.0 (1.2)	0.02
	Adult (18, 50]	82	73.2 (7.8)		13.4 (1.3)	
	Old >50	44	75.4 (6.9)		13.5 (0.9)	
BMI	Normal <25	108	71.5 (7.2)	0.09	13.1 (1.2)	0.01
	Overweight [25, 30]	61	73.1 (6.7)		13.2 (1.1)	
	Obese >30	47	73.9 (6.6)		13.7 (1.3)	
Gender	Female	120	72.5 (6.6)	0.3	13.3 (1.3)	0.6
	Male	96	71.5 (7.5)		13.2 (1.2)	
Age + Race	White&Young	52	69.2 (5.4)	<0.001	12.7 (1.3)	0.001
	White&Adult	33	70.2 (4.7)		12.9 (0.6)	
	White&Old	21	74.3 (8.5)		13.4 (1.0)	
	Black&Young	38	73.4 (5.4)		13.4 (1.1)	
	Black&Adult	49	75.3 (8.9)		13.8 (1.5)	
	Black&Old	23	76.4 (5.0)		13.7 (0.8)	

FIGURE 2 Comparison of AGR and RDW among race, age, BMI and gender groups. A, Mean (red), SD (light blue), and 95% confidence interval (blue) of AGR and RDW in different subgroups. B, Numerical comparisons. AGR, apparent glycation ratio; BMI, body mass index; RDW, red cell distribution width

respectively ($p < .001$). We further found that age, but not gender, had an effect on AGR (Figure 2). In particular, average AGR values increase in the older age groups. Comparing the youngest and oldest age groups, the AGR difference is 4.5 ml/g or 6%. The AGR differences between racial groups are of a largely similar magnitude, corresponding to about 0.45% (approximately 5 mmol/mol) difference in HbA1c at mean glucose of 154 mg/dl. The effects of race and age appeared to be additive, with old black individuals having the highest AGR of 76.4 ± 5.0 ml/g compared with young white individuals having the lowest AGR of 69.2 ± 5.4 ml/g. In contrast to race and age, males and females had similar AGR at 72.5 ± 6.6 and 71.5 ± 7.5 ml/g, respectively ($p = .30$). These group differences, except between genders, are statistically and clinically significant (Figure 2A).

Given the increased complication rate in overweight individuals with T1D,³² we analysed the relationship between body mass index (BMI) and AGR, and no statically significant differences were found comparing normal weight, overweight and obese (BMI ≤ 25 , >25 -30 and >30 kg/m², respectively). However, there seems to be a trend of increasing AGR with higher BMI. This data set may be underpowered to detect the difference.

3.5 | Between-group and within-group apparent glycation ratio variations

We found interindividual variance within each group to be at least four times larger than the average between-group variance. This can be seen by comparing the within-group and between-group variance. In Figure 2B, for example, the least within-group AGR SD is 6.2 and 5.8 ml/g in racial and age groups, respectively. These SD values correspond to 38.4 and 33.6 ml²/g² in variances. These numbers are four times larger than the between-group mean variances of 9.2 and 3.2 ml²/g² for racial and age groups, respectively.

3.6 | Associations between apparent glycation ratio and red cell distribution width

Among the age, gender and racial groups, RDW showed a similar trend to AGR (Figure 2), suggesting a relationship between the two measures. Additive effects of race and age are observed with AGR and RDW, evidenced by similar mean values for the oldest white group and the youngest black group.

RDW can reflect RBC lifespan/turnover, although it is also affected by pathological conditions.²⁸ As AGR is the product of RBC lifespan and apparent haemoglobin glycation rate, AGR and RDW should be associated with each other. We see good concordance on group average level, as shown in Figure 2. The regression analysis produced $R = 0.2$, a weak positive correlation.

4 | DISCUSSION

To our knowledge, this is the first study to investigate the relationship between average glucose and HbA1c across different groups of

individuals with T1D using a recently developed methodology. We show that both race and age modulate this relationship, while gender has no effect. Importantly, we also show large within-group inter-individual differences in this relationship, which has future clinical implications.

The observed non-linear relationship between fasting glucose and HbA1c was originally attributed to a Michaelis-Menten saturation type reaction between glucose and haemoglobin.^{33,34} As the importance of good glucose control in diabetes became well-established, the observed dynamic range of glucose decreased, and various linear approximations have been utilized to characterize the relationship between glucose and HbA1c.^{7,35} Meanwhile, the Michaelis constant for glucose and GLUT1 (K_M) has been measured to be approximately 472 mg/dl,³¹ which affects the curvature of the relationship between glucose and HbA1c. Our methodology estimated K_M at 464 mg/dl, which is in close agreement with the experimentally reported value, adding strength to the equation used to make our calculations. Moreover, our methodology is consistent with a non-linear relationship between glucose and HbA1c, thus circumventing average glucose artefacts with the use of linear relationship models.

Our data show that AGR values are proportional to HbA1c under a given glucose level. Using AGR, we provide an explanation for the previously reported racial differences in the relationship between HbA1c and glucose levels.²⁰ Our findings are not only supportive of the main findings of the original analysis but also to our knowledge provide, for the first time, an insight into the reasons HbA1c shows ethnic variability despite similar average glucose levels. An additional observation is that age has a similar effect to race and that the two have an additive effect. Regression analysis shows an independent association of AGR with age and race, further supporting distinctive roles for each in determining the relationship between average glucose and HbA1c. Similarly, age and race are also independently associated with RDW. Because RDW correlates with RBC lifespan, race and age probably affect AGR through RBS lifespan change. Clinically, HbA1c can be more than 0.7% (7 mmol/mol) higher in an older black adult than a younger white child for an identical glucose exposure, and this has clear clinical implications. For example, the higher HbA1c in a black adult may result in overtreatment and precipitation of hypoglycaemia, which is associated with adverse outcomes, particularly in older people.¹¹ Conversely, the relatively 'good HbA1c' in a white child may give a false sense of security, resulting in undertreatment when it is well established that early glycaemic control is crucial in this group.³⁶ It should be noted that it is not only a 'group effect', as we show that inter-individual variations in the HbA1c-average glucose relationship are even larger than the between-group differences.³⁷

Our T1D cohort had a median AGR of 72.0 ml/g, which is greater than the reference value for individuals without diabetes at 65.1 ml/g, indicating an approximately 0.7% higher HbA1c at a mean glucose of 154 mg/dl in our patient cohort. This suggests that hyperglycaemia per se, or other unidentified factors, can alter the average glucose-HbA1c relationship. One potential mechanism is altered GLUT1 activity secondary to hyperglycaemic exposure of RBC,³⁸ although there is probably more than a single mechanism involved.³⁹

TABLE 2 Adjust HbA1c target by AGR for equivalent average glucose

A1c target (%)	AGR (ml/g)	Adjusted A1c target (%) based on AGR				
		6.0	6.5	7.0	7.5	8.0
60	60	5.5	6.0	6.5	7.0	7.5
	65	6.0	6.5	7.0	7.5	8.0
	70	6.4	7.0	7.5	8.1	8.6
	75	6.8	7.4	8.0	8.6	9.2
	80	7.2	7.9	8.5	9.1	9.7

Note: HbA1c targets were assigned with a reference AGR of 65.1 ml/g during the calculation.

Abbreviations: AGR, apparent glycation ratio; HbA1c, glycated haemoglobin.

Given between-group differences in AGR as well as inter-individual differences within each group, addressing glycaemic control according to a uniform HbA1c target can lead to inappropriate management decisions. For example, at a target HbA1c of 7%, an individual with an AGR of 80 mg/dl will have an average glucose of 117 mg/dl, while another individual with an AGR of 60 will display a much higher average glucose level at 172 mg/dl. This makes the second person at much higher risk due to high glucose exposure of organs susceptible to diabetes complications. This calls for the development of a personalized HbA1c target to optimize glycaemic care. In particular, Table 2 shows how a personal HbA1c target should be adjusted by AGR based on Equation (1). Some may argue that given the various issues with HbA1c accuracy, this glycaemic marker should be replaced entirely by CGM-derived metrics.⁴⁰ However, there are two caveats to this approach; first, the ideal time in range has only undergone limited validation, and more evidence for this glycaemic marker is needed. Second, it is difficult to place all patients with diabetes on CGM due to financial constraints. Our methodology will help to estimate AGR and adequate HbA1c levels using intermittent CGM, which would be more affordable. It is worth noting that while estimated AGR is affected by age, it is stable for at least 200 days,²² provided there are no major changes in health, such as new-onset anaemia or renal failure. We should acknowledge, however, that the value of our personalized HbA1c target would need validation in prospective clinical outcome studies before widely adopting this measure in routine clinical practice.

Given that AGR represents a product of personalized glucose uptake and RBC lifespan, we also analysed the correlation with RDW, a biomarker associated with RBC lifespan.^{28,29} We confirmed previous research indicating a correlation between RDW and age,⁴¹⁻⁴⁴ and we showed a relationship for AGR with age but not gender. Moreover, AGR and RDW showed similar trends across the age groups, and a significant, albeit weak, correlation was detected between the two measures. The presence of a correlation is not surprising given the association between RDW and RBC lifespan^{28,29} and the fact that the latter is part of the AGR calculations.

Strengths of the work include the novel approach, simplicity of the calculations and the adequate power to detect small differences in AGR. However, there are caveats to be highlighted. Limited ranges of HbA1c in T1D were analysed (6–12%), and therefore it is unclear whether our data still apply to extremes of HbA1c or T2D. Moreover, direct analysis of RBC lifespan or glucose uptake was not undertaken, which would have helped validate our model further. However, this is highly challenging and will require a separate piece of work to investigate the in vivo/ex vivo technical feasibility of such measurements.

5 | CONCLUSIONS, PRACTICAL APPLICATIONS AND FUTURE DIRECTIONS

AGR values differ between individuals and across various groups of patients with T1D. Moreover, our analysis confirmed the non-linear relationship between steady-state glucose and HbA1c, casting doubts over the validity of models using linear calculations. Importantly, AGR appears to be a good marker of glycation tendency and is individual-specific. Therefore, AGR can help identify variations in the relationship between HbA1c and average glucose, in turn optimizing glycaemic care by escalating therapies in those who are undertreated and relaxing glycaemic management in those prone to hypoglycaemia. This study analysed individuals with T1D and while the same will probably apply to those with T2D, a separate study is required to confirm the validity of this approach in the T2D population.

AUTHOR CONTRIBUTIONS

YX developed and implemented all computations. All authors were involved in the design of the research, analysis and interpretation of the data. All authors worked collaboratively to review and prepare the final manuscript.

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CONFLICT OF INTEREST

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PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14763>.

DATA AVAILABILITY STATEMENT

Data is available on request from the authors. The data supporting this study's findings are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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