The Fallacy of Average: How Using HbA$_{1c}$ Alone to Assess Glycemic Control Can Be Misleading

HbA$_{1c}$ is a valuable metric for comparing treatment groups in a randomized trial, for assessing glycemic trends in a population over time, or for cross-sectional comparisons of glycemic control in different populations. However, what is not widely appreciated is that HbA$_{1c}$ may not be a good indicator of an individual patient’s glycemic control because of the wide range of mean glucose concentrations and glucose profiles that can be associated with a given HbA$_{1c}$ level. To illustrate this point, we plotted mean glucose measured with continuous glucose monitoring (CGM) versus central laboratory–measured HbA$_{1c}$ in 387 participants in three randomized trials, showing that not infrequently HbA$_{1c}$ may underestimate or overestimate mean glucose, sometimes substantially. Thus, if HbA$_{1c}$ is to be used to assess glycemic control, it is imperative to know the patient’s actual mean glucose to understand how well HbA$_{1c}$ is an indicator of the patient’s glycemic control. With knowledge of the mean glucose, an estimated HbA$_{1c}$ (eA1C) can be calculated with the formula provided in this article to compare with the measured HbA$_{1c}$. Estimating glycemic control from HbA$_{1c}$ alone is in essence applying a population average to an individual, which can be misleading. Thus, a patient’s CGM glucose profile has considerable value for optimizing his or her diabetes management.

As expounded by Todd Rose in his book The End of Average (1), the mean of a measurement made among a large number of individuals is relevant for describing a population or group but often is not applicable for a given individual and can be misleading. Hemoglobin A$_{1c}$ (HbA$_{1c}$) provides a good example of this. HbA$_{1c}$, which reflects blood glucose concentrations over 3–4 months, is a valuable metric for comparing treatment groups in a randomized trial, for assessing glycemic trends in a population over time, or for cross-sectional comparisons of glycemic control in different populations, and it is the only metric of glycemic control that has been strongly associated with chronic diabetic vascular complications. However, it has been debated whether, for an individual patient, the HbA$_{1c}$ level is the best marker for complication risk or whether the level of glycemia with which the HbA$_{1c}$ is associated is an equal or better marker of the risk of complications. Well recognized is the fact that HbA$_{1c}$ may not accurately reflect glycemic control in the presence of a hemoglobinopathy, hemolytic anemia, or other conditions that affect red blood cell life span or interfere with glucose binding to hemoglobin. However, what is not widely appreciated is that even when no such diagnosed condition is present, HbA$_{1c}$ may not be a good indicator of an
individual’s glycemic control because of the wide range of mean glucose concentrations and glucose profiles that can be associated with a given HbA1c level. It has been postulated that this mean glucose–HbA1c discordance is due to interindividual variation in red blood cell life span (2,3).

This distinction in utilizing HbA1c to compare groups versus its use in determining glycemic control for an individual was illustrated in a recent study we and others conducted assessing racial differences in the mean glucose–HbA1c relationship (4). The study showed that on average HbA1c levels in blacks are about 0.4% (4.4 mmol/mol) higher than those of whites for a given mean glucose concentration determined with continuous glucose monitoring (CGM). However, importantly the data also showed that the interindividual variation in HbA1c for a given mean glucose concentration within race substantially exceeds the average degree of variation between races.

The wide range of mean glucose concentrations associated with a given HbA1c level is not a new observation. It has been known since at least the 1990 publication of Yudkin et al. (5) and has been consistently demonstrated in numerous studies in individuals with prediabetes, type 1 diabetes, and type 2 diabetes (6–13), including the A1c-Derived Average Glucose (ADAG) study, which produced the widely used conversion table to estimate mean glucose for an HbA1c level (14).

The ADAG study was conducted in 2006–2007, utilizing CGM, which was not as accurate as current generation CGMs, as well as blood glucose meter measurements to determine the mean glucose concentration. The analysis was conducted on a data set with a median of 13 days of CGM measurements plus 39 days of fingerstick blood glucose measurements. To assess the mean glucose–HbA1c relationship with current CGM technology and a greater amount of data, we pooled data collected in 387 participants (age range 20–78 years, 83% white, 315 with type 1 diabetes and 72 with type 2 diabetes) in three randomized trials using the Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, pooled for the analyses herein are refs. 15, 16, and 28 (ClinicalTrials.gov identifiers NCT02282397, NCT02282397, and NCT02258373, respectively). 195% CI for a patient’s mean glucose concentration for a measured HbA1c level.

Table 1—Range of mean glucose concentrations for observed HbA1c levels in pooled data from three recent studies* and the ADAG study

| HbA1c, % (mmol/mol) | Estimated mean glucose concentration (mg/dL) for a given HbA1c, 95% CI† |
|--------------------|-------------------------------------------------|
| Current study* (N = 387) | ADAG study (N = 507) |
| 6 (42) | 101–163 | 100–152 |
| 7 (53) | 128–190 | 123–185 |
| 8 (64) | 155–218 | 147–217 |
| 9 (75) | 182–249 | 170–249 |
| 10 (86) | 209–273 | 193–282 |

*The three studies from which data were obtained using the Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, pooled for the analyses herein are refs. 15, 16, and 28 (ClinicalTrials.gov identifiers NCT02282397, NCT02282397, and NCT02258373, respectively). 195% CI for a patient’s mean glucose concentration for a measured HbA1c level.

As shown in Fig. 1, in the compiled data from the three studies, there is a wide range of mean glucose concentrations for a given HbA1c level. For an HbA1c of 8.0% (64 mmol/mol), the 95% prediction interval for mean glucose concentration is 155 to 218 mg/dL, substantially overlapping the CI for HbA1c of 7.0% (53 mmol/mol) of 128 to 190 mg/dL and HbA1c of 9.0% (75 mmol/mol) of 182 to 249 mg/dL. So, an HbA1c of 8.0% (64 mmol/mol) could be associated with good, fair, or poor glycemic control as judged by potential mean glucose levels of 128 to 249 mg/dL.

Figure 1—Plot of CGM-measured mean glucose concentration vs. laboratory-measured HbA1c. The shaded area represents the 95% prediction interval (analogous to an individual CI) for a patient’s mean glucose concentration for a measured HbA1c level, demonstrating the wide range of mean glucose concentration values that are possible for any HbA1c value.

Figure 2—Plot of laboratory-measured HbA1c vs. CGM-measured mean glucose concentration used to derive eA1C. The shaded area represents the 95% CI for the population mean HbA1c estimated from a mean glucose concentration. Equation to estimate HbA1c for a given mean glucose concentration: eA1C = 3.38 + 0.02345 × [mean glucose]. (23,24)
Figure 3—AGPs from four patients with laboratory-measured HbA1c of 8.0%. AGPs are shown for four adults with type 1 diabetes using multiple daily injections of insulin, all with an HbA1c of 8.0% from the same central reference laboratory. Displayed are 2 weeks of CGM data (up to 288 CGM values/day) for each patient measured just prior to the HbA1c laboratory test. The CGM is displayed as a modal or standard day. Shown are the median lines of all the glucose values over 2 weeks, the 25% and 75% lines (enclosing the shaded interquartile range [IQR]), and the 10% and 90% lines (dashed). The hatched area is the target glucose range of 70–180 mg/dL. Clinical note 1: Although each of the four patients has the same HbA1c, the AGP patterns are very different and would suggest different insulin and/or lifestyle interventions. Clinical note 2: The mean glucose varies from 156 to 195 mg/dL among the four patients. For patients 1 and 2, eA1C (8.4%) based on mean CGM glucose (195 mg/dL) is slightly higher than the measured HbA1c (8.0%), indicating that the measured HbA1c is slightly underestimating the mean glucose and that despite the same mean glucose, the daily pattern varies considerably. For patients 3 and 4, eA1C (7.0% and 7.3%, respectively) based on the mean CGM glucose (156 and 163 mg/dL, respectively) is substantially lower than the measured HbA1c (8.0%), indicating that the measured HbA1c is overestimating the mean glucose. Again, despite similar mean glucose concentrations, the daily pattern has considerable variation between the two patients. Avg, average.
These results are quite similar to the results of the ADAG study (Table 1). Thus, estimating glycemic control by HbA1c alone may not be accurate for some patients. As a result, utilizing HbA1c alone to judge health care provider performance in treating patients with diabetes may be problematic. The potential impact of mean glucose–HbA1c discordance is illustrated in the post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD).
Using HbA1c Alone to Assess Glycemic Control

A study by Hempe et al. (17) showed that HbA1c lower than predicted from fasting glucose concentration and that such subjects were more likely to have experienced severe hypoglycemia than those with an HbA1c lower than predicted. Regardless of whether this finding is a possible explanation for the ACCORD mortality results, this analysis illustrates the problem and in some cases potential danger of determining a patient’s treatment regimen and glycaemia goal from HbA1c, alone without knowledge of the patient’s mean glucose–HbA1c relationship and glucose profile.

**IMPLICATIONS FOR CLINICAL PRACTICE**

The best way to determine whether a given HbA1c might be over- or underestimating a patient’s level of glycemic control is with CGM. CGM technology has advanced to where this can be done accurately and easily. For patients not already using CGM, a blinded CGM sensor could be worn once to compute a mean glucose concentration that can be compared with the patient’s HbA1c. Ideally CGM data should be obtained for at least 14 days immediately preceding the measurement of HbA1c during a period when diabetes treatment and glycemic control are reasonably stable (18). Several studies have demonstrated that an individual’s mean glucose–HbA1c relationship tends to be reasonably constant over time (7,19–22). Although interval blinded CGM is useful for identifying patterns of glycemic control, a single blinded 14-day CGM wear to measure mean glucose concentration should be sufficient to estimate HbA1c to determine how well the actual HbA1c measurement estimates overall glycemic control for the patient. We recognize that this may not be realistic currently for all patients with diabetes, especially those with type 2 diabetes, but as sensor technology advances, that could become part of standard practice.

With knowledge of an individual’s mean glucose concentration, a CGM-estimated HbA1c can be determined from the plot shown in Fig. 2 or by plugging the mean glucose concentration into the following formula: 3.38 + 0.02345 [mean glucose] (23,24). Then, to inform how well an HbA1c measurement estimates the mean glucose concentration for a patient, the estimated HbA1c (eA1C) can be compared with the observed HbA1c, which has been referred to as the hemoglobin glycation index (observed HbA1c minus predicted HbA1c) (9).

While potentially better than HbA1c in understanding an individual patient’s glycemic control, mean glucose itself is an average, and different degrees of glycemic variability and many different glycemic patterns could produce similar mean glucose concentrations and similar HbA1c levels. Figure 3 shows 2 weeks of CGM data (up to 288 sensor glucose measurements/day) displayed as a modal day or an ambulatory glucose profile (AGP) for four patients with type 1 diabetes using multiple daily injections of insulin. While each patient has a central laboratory–measured HbA1c of 8%, the AGP glucose patterns vary greatly and would each lead to different clinical advice for lifestyle changes or insulin adjustments. This is where retrospective review of CGM data has considerable benefit. CGM profiles provide far more information than just the mean glucose concentration by identifying patterns of hyperglycemia and hypoglycemia as well as potentially dangerous high or low glucose concentrations that are often missed with self-monitoring of blood glucose. The results of secondary analyses of two major studies (the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE] trial and the Atherosclerosis Risk in Communities [ARIC] Study) (25,26) that found an association between hypoglycemia and cardiovascular events emphasize the importance of understanding a patient’s glucose profile with CGM to potentially identify patients who may be at high risk for these events. Thus CGM by providing more clinical insights than HbA1c or self-monitoring of blood glucose measurements can help optimize and personalize glucose control and diabetes management (27).

**CONCLUSIONS**

We have written this Perspective to raise awareness of the need to know a patient’s actual mean glucose concentration, ideally by using CGM, if HbA1c is to be used to assess a patient’s glycemic control and make diabetes management decisions. As long as HbA1c is being used to define a glycemic target, we hope that eA1C becomes a standard metric used by clinicians and patients in assessing the level of glycemic control. Beyond that, a patient’s CGM glucose profile, or AGP, has considerable value for optimizing diabetes management. Estimating glycemic control from HbA1c alone is in essence applying a population average to an individual, which can be misleading. In this era of personalized, precision medicine, there are few better examples than this one with respect to the fallacy of applying a population average to a specific patient rather than using specific information about the patient to determine the optimal approach to treatment.

**Funding and Duality of Interest.** Funding from the Leona M. and Harry B. Helmsley Charitable Trust supported in part the analyses performed and the writing of the manuscript and some components of AGP development and evaluation. The National Institute of Diabetes and Digestive and Kidney Diseases (DK108611) supported work to refine the AGP for clinical and research use. R.W.B.’s nonprofit employer has received consultant payments on his behalf from Animas, Insulet, and Tandem and research grants from Novo Nordisk, Boehringer Ingelheim, Takeda, Animas, Dexcom, Bigfoot, and Tandem with no direct personal compensation to R.W.B. R.M.B.’s nonprofit employer has received consultancy payments from Abbott Diabetes Care, Amylin, Bayer, Boehringer Ingelheim, Calibra, Eli Lilly, the Leona M. and Harry B. Helmsley Charitable Trust, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda and grants from Abbott Diabetes Care, Bayer, Becton Dickinson, Boehringer Ingelheim, Calibra, Dexcom, Eli Lilly, the Leona M. and Harry B. Helmsley Charitable Trust, Hygieia, Johnson & Johnson, Medtronic, Merck, National Institutes of Health, Novo Nordisk, Roche, Sanofi, and Takeda with no direct personal compensation to R.M.B. R.M.B.’s employer receives royalties from the Betty Crocker Diabetes Cookbook, and R.M.B. holds stock in Merck. D.M.M.’s nonprofit employer has received research grants from Abbott Diabete Care and Dexcom for which there was no personal compensation. No other potential conflicts of interest relevant to this article were reported.

**References**

1. Rose T. The End of Average: How We Succeed in a World That Values Sameness. New York, Harper Collins, 2015
2. Cohen RM, Franco RS, Khera PK, et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood 2008; 112:4284–4291
3. Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. Sci Transl Med 2016;8:359ra130

4. Bergenstal RM, Gal RL, Connor CG, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. Ann Intern Med. 13 June 2017 [Epub ahead of print]; DOI: 10.7326/M16-2596

5. Yudkin JS, Forrest RD, Jackson CA, Ryle AJ, Davies S, Gould BJ. Unexplained variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Diabetologia 1990;33:208–215

6. Cohen RM, Haggerty S, Herman WH. HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? J Clin Endocrinol Metab 2010;95:5203–5206

7. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care 2003;26:163–167

8. Wilson DM, Kollman; Diabetes Research in Children Network (DirecNet) Study Group. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. Diabetes Care 2008;31:381–385

9. Hempe JM, Gomez R, McCarter RJ Jr, Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. J Diabetes Complications 2002;16:313–320

10. Wilson DM, Xing D, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Hemoglobin A1c and mean glucose in patients with type 1 diabetes: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Care 2011;34:540–544

11. Kilpatrick ES, Rigby AS, Atkin SL. Variability in the relationship between mean plasma glucose and HbA1c: implications for the assessment of glycemic control. Clin Chem 2007;53:897–901

12. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c: analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. Diabetes Care 2002;25:275–278

13. Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: research gaps and future directions. Diabetes Care 2016;39:1299–1306

14. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1C-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478

15. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378

16. Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous glucose monitoring vs usual care in type 2 diabetes patients on multiple daily insulin injections: a randomized trial. Ann Int Med. In press

17. Hempe JM, Liu S, Myers L, McCracher JB, Fonseca V. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care 2015;38:1067–1074

18. Xing D, Kollman C, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther 2011;13:351–358

19. Argento NB, Nakamura K, Sala RD, Simpson P. Hemoglobin A1C, mean glucose, and persistence of glycation ratios in insulin-treated diabetes. Endocr Pract 2014;20:252–260

20. Nayaq AU, Holland MR, Macdonald DR, Neill A, Singh BM. Evidence for consistency of the glycation gap in diabetes. Diabetes Care 2011;34:1712–1716

21. Rodriguez-Segade S, Rodriguez J, Garcia Lopez JM, Casanueva FF, Camiña F. Estimation of the glycation gap in diabetic patients with stable glycemic control. Diabetes Care 2012;35:2447–2450

22. Wilson DM, Xing D, Cheng J, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes Care 2011;34:1315–1317

23. Jaeb Center for Health Research. HbA1c estimator [Internet]. Available from https://www.jaeb.org/a1c/. Accessed 3 June 2017

24. International Diabetes Center, Jaeb Center for Health Research. Links: eA1C calculator. HbA1c estimator [Internet]. Available from www.agpreport.org/agp/links. Accessed 3 June 2017

25. Heller SR, Bergenstal RM, White WB, et al.; EXAMINE Investigators. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. Diabetes Obes Metab 2017;19:664–671

26. Lee AK, Warren B, Lee CJ, et al. Association of severe hypoglycemia with cardiovascular disease and all-cause mortality in older adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2017;135:A43

27. Bergenstal RM, Ahmann AJ, Bailey T, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). Diabetes Technol Ther 2013;15:198–211

28. Aleppo G, Ruedy KJ, Riddlesworth TD, et al.; REPLACE-BG Study Group. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. Diabetes Care 2017;40:538–545