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SYMPOSIUM

The Correlation of Hemoglobin A1c to Blood Glucose

Ken Sikaris, B.Sc., M.B.B.S., FRCPA, FAACB

Abstract

The understanding that hemoglobin A1c (HbA1c) represents the average blood glucose level of patients over the previous 120 days underlies the current management of diabetes. Even in making such a statement, we speak of "average blood glucose" as though "blood glucose" were itself a simple idea. When we consider all the blood glucose forms—arterial versus venous versus capillary, whole blood versus serum versus fluoride-preserved plasma, fasting versus nonfasting—we can start to see that this is not a simple issue.

Nevertheless, it seems as though HbA1c correlates to any single glucose measurement. Having more than one measurement and taking those measurements in the preceding month improves the correlation further. In particular, by having glucose measurements that reflect both the relatively lower overnight glucose levels and measurements that reflect the postprandial peaks improves not only our ability to manage diabetes patients, but also our understanding of how HbA1c levels are determined. Modern continuous glucose monitoring (CGM) devices may take thousands of glucose results over a week. Several studies have shown that CGM glucose averages account for the vast proportion of the variation of HbA1c.

The ability to relate HbA1c to average glucose may become a popular method for reporting HbA1c, eliminating current concerns regarding differences in HbA1c standardization. Hemoglobin A1c expressed as an average glucose may be more understandable to patients and improve not only their understanding, but also their ability to improve their diabetes management.

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Introduction

Diabetes is caused by an absolute or functional lack of insulin, which leads to increased glucose levels outside the cell. High concentrations of glucose can increase the glycation of common proteins such as hemoglobin, forming Hemoglobin A1c (HbA1c). However, it is important to note that HbA1c is neither considered dysfunctional nor harmful.[1] Nevertheless, the concentration of HbA1c predicts diabetes complications because it reflects more harmful glycation sequelae of diabetes, such as retinopathy and nephropathy, which are understood to be due to harmful advanced glycation end products.

Author Affiliation: Sonic Health–Melbourne Pathology, Victoria, Australia

Abbreviations: (CGM) continuous glucose monitoring, (CGMS) continuous glucose monitoring system, (CV_i) intraindividual coefficient of variation, (DCCT) Diabetes Control and Complications Trial, (HbA1c) hemoglobin A1c, (IFCC) International Federation of Clinical Chemistry

Keywords: continuous glucose monitoring, hemoglobin A1c, mean blood glucose, plasma glucose, serum glucose

Corresponding Author: Ken Sikaris, FRCPA, Sonic Health–Melbourne Pathology, 103 Victoria Parade, Collingwood, Victoria, Australia 3066; email address ken.sikaris@mps.com.au

Hemoglobin A1c is known to correlate with blood glucose levels over the lifetime of the red blood cell, which is approximately 120 days.[2,3] Although red cell survival may show subtle differences between diabetes patients and nondiabetes patients which could be considered,[4,5] the fundamental understanding is that blood glucose levels determine HbA1c levels, and this underpins the value of HbA1c as the current gold standard for clinical monitoring of diabetes.

What Exactly Is Blood Glucose?

The simple term "blood glucose" is surprisingly complex. First, blood glucose can be highly variable, increasing rapidly after a carbohydrate meal and then falling to the relatively steady fasting state. The fasting state is itself a dynamic state, where the removal of glucose from the blood is at first balanced by glycogen breakdown and then supported by gluconeogenesis. Second, as Gambino has emphasized, our estimation of blood glucose is problematic, and estimates can differ by up to 14% from laboratory to laboratory, reflecting a suboptimal state of the art when it comes to glucose measurement.[6] This could be improved by calibration and preservation of stored samples to inhibit *in vitro* glycolysis. However, when it comes to the measuring of glucose levels in diabetes patients, we should always clearly define the matrix we are referring to.

Whole Blood Versus Plasma

Despite whole blood glucose being the most common measurement in medicine worldwide, we can begin this discussion with the observation that there is no internationally recognized reference method for the measurement of blood glucose.[7] This difficulty stems from the composition of blood, being predominantly a mixture of plasma and the red blood cell hematocrit. Plasma is largely water (93%), the rest being accounted for by protein and lipids. Red blood cells are also largely water (71%), and water-soluble glucose can diffuse freely into that compartment. The concentration of glucose in the red cell is 0.763 of the concentration of glucose in plasma (71%/93%). The higher the hematocrit, the more the overall blood glucose concentration will reflect the red cells and vice versa. The difficulty in standardizing whole blood glucose measurements relies on this fact, and not surprisingly, the use of whole blood glucose standards improves the agreement of whole blood meters[8] as does the simultaneous measurement of hematocrit.[9]

For the aforementioned reasons, the standardization of whole blood glucose measurements has been made against a more convenient and reproducible standard: plasma glucose.[10–12] As red cells are 71% water and plasma is 93% water, whole blood is typically 84% water, so the ratio of plasma to whole blood (93%/84%) is defined as 1.11. Whole blood glucose values can effectively be made equivalent to plasma glucose values by increasing them by 11%. While discrepancies were common in the past,[13] the introduction of this factor improves the whole-blood-versus-plasma agreement.[14]

Arterial Versus Venous Glucose

As glucose is usually taken up by the cells, we expect that venous glucose is approximately 5–10 mg/dl lower than arterial glucose. However, the arteriovenous gradient will depend on the insulin level that determines the degree of glucose uptake.[15] The decrease also correlates with the difference in oxygen saturations.[16] Not only may this decrease vary, but glucose may even be generated in peripheral tissues, most notably in muscle, during critical illness and released into the venous system.[17] Nevertheless, an 8% decrease is generally expected (e.g., arterial glucose 110 mg/dl = venous glucose 100 mg/dl).

Arterial Versus Capillary Glucose

Capillary blood refers to the blood that would ooze from the tissue following a finger prick. This blood is typically red (not blue) and more closely reflects oxygenated arterial blood than venous blood. Even in critical illness, capillary blood glucose usually reflects arterial blood glucose;[18] however, discrepancies can occur,[19,20] suggesting that, in this critical scenario, arterial levels may be more reliable. Discrepancies between arterial and capillary blood glucose values are probably due to a combination of reasons, including poor peripheral perfusion as well as the suboptimal analytical performance of some point-of-care testing devices in this setting.[21]

Some of the most common causes of inaccurate glucometer readings in any setting include lack of periodic meter technique evaluation, difficulty using wipe meters, incorrect use of control solutions, lack of hand washing, and using unclean meters.[22] Though the use of glucometers for monitoring of blood glucose can be advocated, they are still not recommended for the initial diagnosis of diabetes mellitus.[23]

Finally, capillary glucose measurements are usually from the fingertip. Capillary samples taken from sites with a poorer blood flow (e.g., thigh or forearm) may show slower responses to rising glucose levels and be associated with discrepancies.[24,25]

Venous Plasma (Laboratory) Versus Capillary Whole Blood (Meter)

We can now compare the two most common methods of glucose measurement. First, whole blood glucose meters should be calibrated to give venous plasma equivalents (as previously discussed). However, because capillary samples reflect arterial blood, they would be expected to be 8% higher than venous plasma. Criteria for the diagnosis of diabetes generally reflect this, as a diagnostic 2 h oral glucose tolerance test venous plasma level of 200 mg/dl is 8% higher for capillary whole blood/plasma (>220 mg/dl), but this continues to cause some confusion.[26]

Interstitial Glucose Versus Arterial Glucose

Interstitial glucose measurement refers to subcutaneous glucose sensors that are not placed within blood vessels. Although these sensors are not measuring blood glucose levels directly, interstitial glucose levels generally have good agreement with arterial levels.[27] It is commonly believed that interstitial glucose levels lag approximately 15 min behind arterial levels due to the time required for glucose to diffuse into the interstitial space. However, studies suggest that this lag may be due partly to amperometric sensor response times (generally less than 1.5 min) and even more largely due to digital averaging by the devices (for example, a simple three-point moving average on a signal obtained every 5 min will smooth the response but take 15 min to reach steady state).[28] In any event, the interstitial devices are usually calibrated against whole blood glucose capillary measurements, which are in turn standardized against plasma glucose equivalents. This ultimately results in interstitial glucose levels that generally correlate with blood glucose values measured in the laboratory.[24]

Hemoglobin A1c Correlations against Single Glucose Values

Materials and Methods

Data were extracted from a large private pathology database (Melbourne Pathology). Hemoglobin A1c was measured by the BioRad Variant Turbo II method, and glucose was measured on a Roche Modular analyzer using glucose oxidase methodology.

During 2007, there were 89,302 HbA1c measurements, and 50,852 cases had a glucose sample taken at the same time. The glucose sample types were 40,928 sodium fluoride/oxalate venous plasma (33,563 fasting, 3792 nonfasting AM, and 3573 nonfasting PM) and 9924 unpreserved serum (7053 fasting, 1502 nonfasting AM, 1369 nonfasting PM).

Data were also extracted for 2116 oral glucose tolerance tests (75 gm) that also had HbA1c taken at the same time. There were no method changes in HbA1c or glucose during the period of this data collection: February 8, 2003, to April 3, 2008.

Hemoglobin A1c Versus Nonfasting Plasma Glucose

Figure 1 shows the correlation between HbA1c and nonfasting plasma glucose on 7365 episodes, where these tests were performed at the same time. The correlation coefficient of $r^2 = 0.50$ ($p < .001$) is remarkably good, considering we are virtually trying to predict the current glucose level using HbA1c, which reflects the average glucose over the past 120 days. Other observations on the correlation include the *x*-axis (abscissa) intercept of a HbA1c between 2% and 3%. It pays to stop and consider what the *x*-axis intercept signifies. It signifies the HbA1c value if glucose levels were zero over the past 120 days. In fact, this is not as irrational as it sounds, as we know that there is a fixed background level of HbA1c that represents a fraction that is not glycated but rather has had its charge altered by carbamylation and/or acetylation of the *N*-terminal valine residue of the hemoglobin molecule. Furthermore, we know that, in the new International Federation of Clinical Chemistry (IFCC) calibration of HbA1c, the conversion between IFCC and National Glycohemoglobin Standardization Program units has a constant factor of 2.15%. In other words, the intercept is physiologically expected.

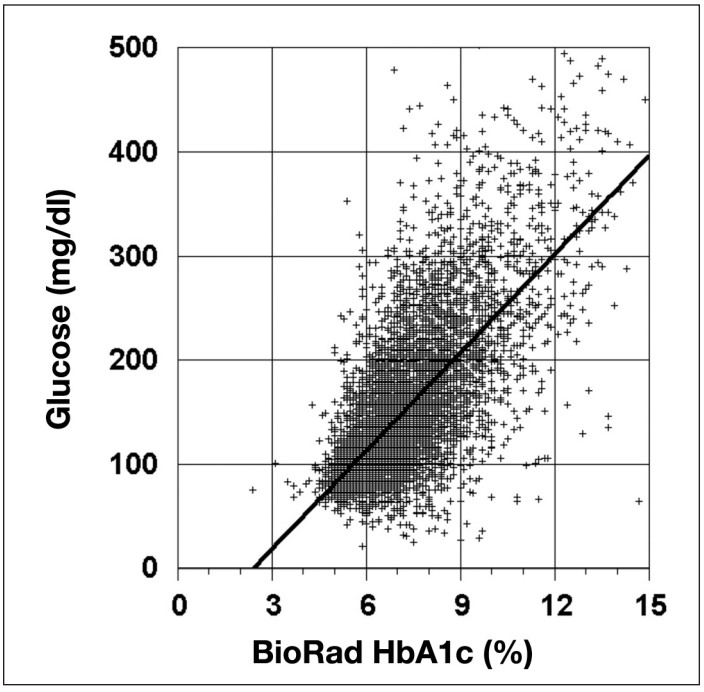

Figure 1. Correlation between hemoglobin A1c and nonfasting plasma glucose on 7365 episodes.

Table 1 shows numerous linear least squares regression equations that separate the HbA1c versus nonfasting plasma glucose relationship into morning (AM) and afternoon (PM), and there are no major differences.

Hemoglobin A1c Versus Fasting Venous Plasma Glucose

Table 1 also lists the correlation of HbA1c with fasting venous plasma glucose. As glucose levels are lower when fasting, the average glucose in these 33,563 samples was expectedly lower (134 mg/dl) compared to the nonfasting samples (150 mg/dl). Furthermore, the slope of the HbA1c versus venous plasma fasting glucose was also decreased (25) compared to the nonfasting slope (33).

The large number of points (33,563) allowed further subanalysis, which reveals that the correlation was no different for the fasting venous plasma samples from women versus men, young versus old (>65), nor in the summer versus winter quarters.

Hemoglobin A1c Versus Venous Serum Glucose

The purpose of this comparison was to investigate the potential effect of *in vitro* glycolysis in the nonfluoride-preserved serum samples. The results for nonfasting and fasting serum samples are also shown in **Table 1**. The results are possibly surprising, as, if anything, the average glucose levels of the serum samples are higher than the fluoride-preserved plasma equivalents, despite having the same average HbA1c. Furthermore, the slope of the HbA1c regression derived from serum samples is also greater than for the fluoride-preserved plasma samples.

There is in fact some debate about the efficacy of fluoride inhibition of glycolysis, as studies have shown that glycolysis will proceed in these plasma samples for an hour or more.[29] Furthermore, the preservation of serum samples may be superior, as glycolysis will stop as soon as the cells are separated by centrifugation.[30] In our laboratory, most serum samples were collected by laboratory-trained staff in accredited collection centers and usually spun within half an hour. This probably leads to better sample preservation as other have also described.[31]

Hemoglobin A1c Versus Glucose Levels from Oral Glucose Tolerance Tests

Table 2 shows the correlation between HbA1c and the single fasting 1 and 2 h fluoride plasma glucose levels taken during a 75 gm oral glucose tolerance test. The correlation between HbA1c and each of the glucose levels is at least as strong as described previously (r^2 between 0.52 and 0.63). While the strongest correlation was against fasting glucose, the 2 h glucose correlations were also strong. Although we might consider the intraindividual

Table 1.
Correlation between Hemoglobin A1c and Various Samples Taken for Glucose at the Same Time

Sample type	State	Time	*n*	Glucose	HbA1c	Correlation			
						r^2	slope	*y* int.	*x* int.
Plasma	Nonfasting	All	7365	150 +/- 75	7.1 +/- 1.6	0.50	33	-89	2.7
		AM	3792	148 +/- 72	7.1 +/- 1.6	0.48	32	-77	2.4
		PM	3573	152 +/- 78	7.1 +/- 1.6	0.52	35	-100	2.9
	Fasting	AM	33,563	134 +/- 49	7.1 +/- 1.4	0.57	25	-46	1.8
	Women		15,308	130 +/- 47	7.0 +/- 1.4	0.58	25	-48	1.9
	Men		18,255	137 +/- 50	7.1 +/- 1.5	0.56	25	-43	1.7
	<65		16,287	138 +/- 55	7.2 +/- 1.7	0.62	26	-50	1.9
	>65		17,276	130 +/- 41	7.0 +/- 1.2	0.48	24	-36	1.5
	Summer		7857	132 +/- 48	7.1 +/- 1.5	0.56	25	-45	1.8
	Winter		8187	135 +/- 49	7.1 +/- 1.5	0.56	25	-45	1.8
Serum	Nonfasting	All	2871	158 +/- 89	7.1 +/- 1.6	0.43	36	-99	2.7
		AM	1502	157 +/- 80	7.1 +/- 1.5	0.45	34	-87	2.5
		PM	1369	159 +/- 97	7.1 +/- 1.7	0.42	38	-110	2.9
	Fasting	AM	7053	135 +/- 51	7.0 +/- 1.4	0.43	26	-46	1.8

Table 2.
Correlation between Hemoglobin A1c and Oral Glucose Tolerance Test Samples Taken at the Same Time

Sample type	State/time	*n*	Glucose	HbA1c	Correlation			
					r^2	slope	*y* int.	*x* int.
Plasma	Fasting	2116	112 +/- 4.3	9.2 +/- 4.3	0.63	22	-27	1.2
	1 h		212 +/- 27		0.52	51	-105	2.1
	2 h		166 +/- 77		0.55	60	-208	3.5
Average	Fasting/1 h		162 +/- 45		0.61	37	-66	1.8
	Fasting/2 h		139 +/- 49		0.64	41	-117	2.9
	Fasting/1 h/2 h		163 +/- 54		0.63	44	-113	2.6
	Weighted[a]		151 +/ -46		0.68	40	-84	2.4

[a] Weighted = (fasting + (1h/20) + (2h/4)

biological variability of fasting glucose to be much smaller [intraindividual coefficient of variation (CV_i = 5.7%)] than 2 h biological variability (CV_i = 16.7%),[32] this is possibly "averaged out" in this large study of 2116 procedures.

Interestingly, the correlation is not improved significantly when HbA1c is correlated against the average of the fasting glucose and combinations of 1 and 2 h glucose levels, although some improvement is seen when 2 and 1 h glucose are given a lower weighting.

Observations on Hemoglobin A1c Versus Single Blood Glucose Correlations from the Literature

While single glucose levels taken at the time of HbA1c measurement may correlate remarkably well, it is perhaps understandable that glucose levels taken a month beforehand may have more directly contributed to the formation of existing HbA1c.[33] Nevertheless, postprandial glucose levels have been found to correlate with HbA1c better than fasting levels.[34,35]

Hemoglobin A1c Correlations against Multiple Glucose Values

Ozmen and colleagues[36] showed that, while any single glucose value (e.g., fasting/postprandial) correlates with HbA1c, better correlations are achieved by averaging the glucose values of an individual. Bonora and associates[37] found that preprandial glucose levels were slightly better than postprandial glucose levels when correlated with HbA1c; however, they also concluded that averaging these values gave the best correlation.

In 1982, Svendson and coworkers[38] reported that the average glucose levels derived from approximately 2 to 300 measurements in each of 18 type 1 diabetes patients correlated almost perfectly (r^2 = 0.96) with "glycosylated hemoglobin."

While most similar studies have been performed in type 1 diabetes patients, Makris and colleagues[39] have shown that average glucometer glucose values in 140 type 2 diabetes patients also correlates with HbA1c over the preceding 12 weeks. They calculated their averages from a minimum of 72 individual measurements taken in the preceding month. The correlation was similarly exceptionally strong (r^2 = 0.87) with a regression equation of mean blood glucose (mg/dl) = 34.74 x HbA1c - 79.21. The strength of their correlation, however, could also be contributed to by the greater stability of glucose levels in type 2 compared to type 1 diabetes patients.

There have been other studies performed that show good correlation of average glucose with HbA1c;[40,41] however, one of the most significant studies was the Diabetes Control and Complications Trial (DCCT). In the DCCT study, 1439 patients had regular glucose measurements 7 times per day that could be compared with their HbA1c.[42] Their regression equation was glucose (mg/dl) = 35.6 HbA1c - 77.3, with r^2 = 0.67 (note similarity to Makris and the slopes and intercepts in **Table 1**).

Kilpatrick and associates[43] reviewed the DCCT findings and found that the HbA1c–glucose relationship seemed to vary between the two treatment arms of the DCCT study, with conventionally treated diabetes patients having higher glucose levels at any given HbA1c than intensively treated diabetes patients. While proposing that fast and slow glycator status may exist, they did, however, recognize that the major weakness of the study was that

the 7-point glucometer measurements did not include any measurements made overnight. They mentioned that a limited data set that included one overnight measurement (8-point glucometer) only showed a slight lowering of the mean blood glucose value. However, it could also have been noted that the contribution of the 8 to 10 h overnight in a 24 h day (33–44%) is significantly more than 1 of 8 glucometer measurements. The differences in the DCCT treatment groups could be easily explained if the intensively treated group had lower overnight glucose levels that were not adequately accounted for—a very likely possibility.

Observations on Hemoglobin A1c Correlations to Continuous Glucose Monitoring

Correlation between Continuous Glucose Monitoring and Glucometer Glucose Values

Continuous glucose monitoring (CGM) relies on calibration (typically from whole blood capillary glucose), and calibration may gradually shift, requiring recalibration, depending on the device. Although accuracy is slightly improved with more calibrations, the timing of the calibrations appears more important, and putting less weight on daytime calibrations for nighttime values and calibrating during times of relative glucose stability may have greater impact on accuracy.[44] Errors in CGM glucose measurement are symmetric but not normally distributed.[45] Gradual sensor weakening may also be observed and could possibly be due to an immune response that could lead to sensor failure.[46]

Studies have generally shown that CGM glucose values agree with glucometer values.[47,48] Boland and coworkers[49] were able to demonstrate that patients with good diabetes control often experienced pronounced fluctuations (hypoglycemia and postprandial hyperglycemia) that were also not evident in the glucometer readings. They showed that, without a continuous glucose monitoring system (CGMS), the fact that most of their type 1 diabetes patients were having at least one hypoglycemic episode over the 3 days of CGM would not have been realized from glucometer readings or HbA1c.

The Diabetes Research in Children Network study group concluded that an important difference between the CGMS and 8-point glucometer testing was that mean glucose levels during the night were lower and the percentage of nighttime values in the hypoglycemic range was greater with the CGMS.[50] **Figure 2** shows a 3-day reading in an 11-year-old girl with type 1 diabetes on 3 insulin injections per day. The tracing illustrates the important features of CGM, including (i) short episodes of hypoglycemia that could be missed by glucometer readings through the daytime (ii) sharp spikes in glucose levels during the day that may also be missed by discrete glucometer testing, and (iii) that the average glucose levels overnight are generally lower than those during the day, a fact that will always lead to seven daily glucometer readings generally overestimating the average glucose level over that whole day. Note that pump therapy will improve postprandial excursions.[51]

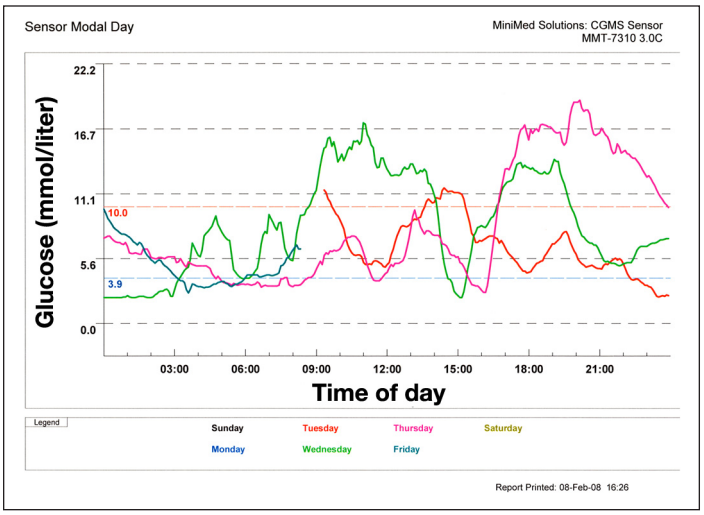

Figure 2. A 3-day reading in an 11-year-old girl with type 1 diabetes on 3 insulin injections per day.

While multiple daily glucometer readings test for the major rhythms (e.g., meals and sleep), mathematical analysis reveals that up to 20 harmonics are required to describe CGM glucose curves.[52] The circadian rhythm of glucose values not only includes meals, activity, and sleeping, but also other events such as the dawn phenomenon, which is a rise in glucose levels due to the morning increase in counter-regulatory hormones such as growth hormone, thyroxin, and cortisol. Continuous glucose monitoring provides this added information and may help patients, especially those with poor glycemic control, achieve better control.[53]

All the studies described in the preceding section found glucometer values to correlate well with HbA1c. The clue to this success comes from the study of Zavalkoff and Polychronakos,[54] which showed strong correlations to CGM for only specific glucometer values. In particular, breakfast glucose values correlate with overnight CGM values, and dinnertime glucometer values correlate with lunch to dinner CGM glucose values.

There is some debate whether the studies to date have shown CGM to be clinically superior to self-monitoring with a glucometer in terms of improving glycemic control and reducing HbA1c further.[55] Nevertheless, CGM allows better identification of marked fluctuations in blood glucose, and this should improve glycemic control.[56]

Correlation between Continuous Glucose Monitoring Glucose and Hemoglobin A1c

Sharp and Rainbow[57] found that the mean sensor glucose value obtained with the Continuous Glucose Monitoring System™ (MiniMed Inc, CA) was highly correlated with the HbA1c at the time of insertion (r^2 = 0.35). It could be surprising if the correlation was much better, as they were trying to predict the average glucose values of the next 2 to 6 days using the HbA1c that reflects the glucose values of the previous 120 days.

Salardi and colleagues[58] made similar observations correlating the area under the glucose curve derived from CGM with HbA1c taken prior to CGM and obtained r^2 values between 0.07 and 0.30, which generally improved as the average glucose levels increased. They concluded that, to improve metabolic control, it is necessary to lower the whole mean 24 h glycemia.

Salardi and associates[58] summarized the superiority of CGMS in correlating with HbA1c by concluding that, "According to our data, it seems that the whole daily glycemia, and not a single glucose value, is an important determinant in the overall glycemic control, as measured by HbA1c."

Nathan and coworkers,[59] in an extensive analysis of CGM, found strong correlations to date between mean glucose (from CGM) and HbA1c (r^2 = 0.79). Their success is attributable to the number of CGM glucose measurements (8000) and, importantly, that they were performed in the month prior to HbA1c measurement. Furthermore, they confirmed that the correlation of the CGM averages were strong over the 12 weeks preceding the HbA1c measurements. Their regression equation (average glucose_{CGM} = 31.5 x HbA1c - 68.6) is slightly lower than the equations derived from glucometers, perhaps reflecting the fact that lower overnight glucose readings are included when using CGM.

Nathan and colleagues were also involved in the A1c-Derived Average Glucose Study Group trial.[60] This trial was established to attempt to fulfill the *a priori* criterion that HbA1c could predict a proper estimate of average glucose within 15% for 90% of patients. This was an exhaustive study across 11 centers in the United States, Europe, Africa, and Asia. They recruited 507 patients with type 1 or type 2 diabetes and performed approximately 2700 glucose measurements per patient. The study fulfilled its purpose and, using a weighted mixture of glucometer and CGM values, recommended a regression equation of average glucose = 28.7 x HbA1c - 46.7, with an excellent r^2 = 0.840. Interestingly, the regression equation using CGM alone was almost as good (r^2 = 0.82) and very similar (average glucose_{CGM} = 28.0 x HbA1c - 36.9). They also concluded that the regression equation did not differ between men or women, type 1 or type 2 diabetes, age, ethnicity, nor smoking status.

Another study using CGM over some but not all the 3 months prior to HbA1c measurement showed a strong but imperfect correlation in children with type 1 diabetes, who typically have higher glucose variability.[61] All these studies show evidence that CGM correlates strongly with HbA1c. While they seem exhaustive, they are imperfect in that (i) they have not monitored glucose continually over 3 months and (ii) the interstitial glucose level estimated by CGM may not technically be identical to the blood glucose level seen by the erythrocyte.

Conclusions

The editorial[62] preceding the A1c-derived average glucose article discusses the importance of the findings in that not only were the *a priori* criteria satisfied, and with an r^2 of 0.84, but the remaining 16% of average glucose that is not explained could be attributed to other undeniable factors, including the variations in HbA1c measurement. Furthermore, the authors noted that the ability to report HbA1c as average glucose may help to avoid the "intolerable confusion" and "mayhem" that would occur with a restandardization of HbA1c to IFCC units (i.e., approximately 2.15% lower). Finally, the authors acknowledged that the expression of HbA1c in average glucose units, familiar to the diabetes patient, not only makes it easier to explain what HbA1c is, but also opens an educational opportunity to discuss discrepancies between the HbA1c-derived average glucose levels and the patient's own measurements.

Patient understanding of HbA1c is poor, especially among type 2 diabetes patients, so strategies to engage patients to know and interpret their HbA1c values should be encouraged within routine clinical practice.[63] This may be the main reason that will determine if HbA1c will be globally expressed as an estimated average glucose.

If this is the case, then it will be important to express in terms of the glucose levels that patients are familiar with. Today it is glucometer values, and until reimbursement issues are resolved, it is unlikely that this will be CGM glucose values in the near future. I could therefore argue that, while CGM probably represents the closest assessment we currently have for average glucose, patient interests may be better served with regression equations that predict their glucometer average.

Logically, glucose levels determine HbA1c levels. Yet even in this article, I discussed and have graphically represented HbA1c as determining the average glucose level. Similarly, I have shown that the x intercept has some meaning ("background HbA1c") and constancy, whereas, in the typically expressed regression equation, the y intercept value has no meaning. However, until we can directly and reliably measure the true average blood glucose over a single day, let alone over the 120-day lifetime of the red blood cell, the best estimates of average blood glucose will come from HbA1c.

Finally, since HbA1c may be the better estimate of average blood glucose than our various attempts to measure blood glucose directly, HbA1c is probably the superior way to monitor long-term glycemic control—this we actually know and do. However, we probably also need to acknowledge that this superiority of HbA1c over discrete blood glucose measurement may also extend to diabetes screening and diagnosis.[64]

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