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REVIEW ARTICLE

Is There a Relationship between Mean Blood Glucose and Glycated Hemoglobin?

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Abstract

Measurement of hemoglobin A1c (HbA1c) is considered the gold standard for monitoring chronic glycemia of diabetes patients. Hemoglobin A1c indicates an average of blood glucose levels over the past 3 months. Its close association with the risk for the development of long-term complications is well established. However, HbA1c does not inform patients about blood glucose values on a daily basis; therefore, frequent measurements of blood glucose levels are necessary for the day-to-day management of diabetes. Clinicians understand what HbA1c means and how it relates to glucose, but this is not the case with patients. Therefore, the translation of the HbA1c results into something more familiar to patients seemed a necessity.

The scope of this article is to review the literature to search for enough scientific evidence to support the idea of a close relationship between HbA1c and mean blood glucose (MBG), and to justify the translation of HbA1c into something that reflects the MBG.

Most studies confirm a close relationship between HbA1c and MBG, although different studies result in different linear equations. Factors affecting this relationship may limit the usefulness and applicability of a unique mathematical equation to all diabetes populations.

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Clinical Importance of Hemoglobin A1c

Monitoring of glycemic status has been considered the cornerstone of diabetes care. The importance of monitoring glycemia has been established by studies proving that there is a direct relationship between mean blood glucose (MBG) and the development and progression of chronic diabetic complications. The results of monitoring are used to assess efficacy of therapy and to guide adjustments in lifestyle to achieve best possible glucose control. The most common tests used today for this purpose are blood glucose and glycated hemoglobin (GHb).[1]

Prior to 1975, routine patient monitoring consisted of glucose and ketone determinations in urine. Since 1975, dramatic changes have taken place in both the methods

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Abbreviations: (ADAG) A1c-Derived Average Glucose, (BV) biological variation, (CGM) continuous glucose monitoring, (DCCT) Diabetes Control and Complications Trial, (eAG) estimated average glucose, (GHb) glycated hemoglobin, (GV) glucose variability, (Hb) hemoglobin, (HbA1c) hemoglobin A1c, (MBG) mean blood glucose, (MPG) mean plasma glucose, (SMBG) self-monitoring of blood glucose, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

Keywords: diabetes, estimated average glucose, glucose, glycated hemoglobin, hemoglobin A1c, mean blood glucose, mean plasma glucoset

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and goals of monitoring. These changes were driven by accumulation of evidence that complications of diabetes were the result of chronic hyperglycemia and by technological advances in portable glucose meters that permitted (since early 1990s) patient self-monitoring of blood glucose (SMBG) to replace urine glucose testing. During the same period, determination of GHb [most commonly hemoglobin A1c (HbA1c)] was found to be a clinically useful measure of glycemic status over the past 3–4 months.

Hemoglobin A1c is a term used to describe a series of stable minor hemoglobin components formed slowly and nonenzymatically from hemoglobin and glucose. The clinical utility of HbA1c as a tool to assess the risk of diabetes complications was confirmed by the publication of the results of the Diabetes Control and Complications Trial (DCCT) and also the United Kingdom Prospective Diabetes Study.[2]

The knowledge that hemoglobin is a heterogeneous molecule is rather old.[3] Since 1955, laboratory methods were established to detect hemoglobin variants and "minor components" in human blood and were named HbA1a, HbA1b, and HbA1c, in order of their elution from a chromatography column.[4,5] Their relation to diabetes was appreciated much later when these minor hemoglobins were detected in diabetic patients[6,7] as well as in non-diabetic adults in a proportion of 1–4%.[8] Structural studies later established that the hemoglobin found in patients with diabetes was indeed identical to HbA1c.[6]

By the mid-1970s, it became clear that HbA1c resulted from a posttranslational modification of hemoglobin A by glucose and was related to fasting plasma glucose, glucose peak during the glucose tolerance test, area under the curve of the glucose tolerance test, and mean glucose levels over the preceding weeks. This relationship is affected by many factors that can be grouped into two broad categories: physiological and analytical. In order to further elucidate this relationship and understand the effect of the physiological factors, we will take a look at the biochemistry of GHb production.

Biochemistry of Glycohemoglobins

Glycation is the nonenzymatic attachment of free aldehyde groups of carbohydrates (such as glucose) to the unprotonated free amino groups of proteins (such as hemoglobin). Glycation alters the structure and function of several soluble and insoluble proteins, as well as the structure and function of isolated basement membrane components. These changes are slow and cumulative, resulting in a long time lag between the diagnosis and the onset and progression of the complications of diabetes mellitus.[9–12]

The Maillard hypothesis suggests that chemical modification of proteins by glucose and subsequent reactions of the adduct may result in products that are directly responsible for many pathological conditions in diabetes.[9,13,14] The reaction of glucose with amino groups in proteins results in the reversible formation of a *Schiff base* or *aldimine*, a labile intermediate, which can undergo irreversible *Amadori rearrangement* to form a ketoamine product (**Figure 1**). Glycation is also a process that appears to be associated with age-related disorders and may be particularly important in the context of long-lived proteins that do not undergo rapid synthesis and turnover.[11,15]

Glycated hemoglobin is not a single molecular entity. There are many various molecular species in human blood, resulting from the many potential glycation sites at the hemoglobin molecule, the different molecular forms of human hemoglobin such as HbA0 ($\alpha 2$-$\beta 2$), HbA2 ($\alpha 2\delta 2$), HbF ($\alpha 2\gamma 2$), and the numerous hemoglobin variants (e.g., HbS, HbC, HbE).

Potential glycation sites of the hemoglobin molecule include the N-terminal amino acid valine of the four polypeptide chains and all free ε-amino groups of lysine residues within the chains. The predominant glycation site is the N-terminal valine residue of the β-chain of the hemoglobin molecule, which accounts for approximately 60% of all bound glucose. The term for this major component is HbA1c. Other glucose molecules can bound to one or more of the 44 glycation sites at the ε-amino groups within the hemoglobin molecule (34% of all bound glucose) or at the N-terminal valine of the α-chain (about 6%).[9,13,14]

There are also some further minor hemoglobin species in human blood that are adducts of other substances

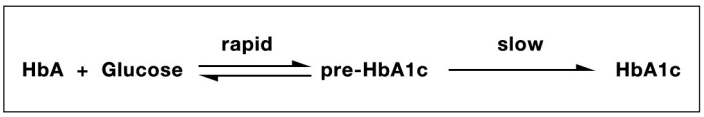

Figure 1. Schematic representation of the course of reaction for the glycation of hemoglobin. Apart from glucose, other sugars and sugar phosphates such as glucose metabolites, fructose, galactose, pentoses and aldehydes react with proteins. Although the reaction rate of some of these compounds is higher than that of glucose, because of their very low concentration in human blood, the concentrations of the adducts are also very low, therefore they are of slight clinical significance under physiological conditions.

to hemoglobin molecule and can interfere in the determination of the GHb depending on the specificity of the analytical method. These are carbamylated and acetylated hemoglobins. The currently used nomenclature can be a bit confusing since they were named according to their elution order in a chromatographic system (**Table 1**).

Table 1.
Terms in Use for Various Hemoglobin Species[a]

Term	Biochemical characteristics
Glycohemoglobin	The sum of carbohydrate adducts to N-terminal amino acids and/or ε-amino acid lysine groups of hemoglobin
HbA1	Sum of various minor hemoglobin species, including HbA1c; the percentage of this biochemically heterogeneous group is method dependent
HbA0	Main component of normal adult hemoglobin, containing two α-chains and two β-chains
HbA1c	Glucose adduct to the N-terminal valine of the β-chain of hemoglobin; major molecular species of glucohemoglobin in human blood
HbA1a1/a2 HbA1b1/b2/b3 HbA1d1/d2/d3 HbA1e	Minor hemoglobin species in human blood named after their elution order from the column in a chromatographic system, biochemically heterogeneous, and not fully characterized

[a] Adapted from Hoelzel and Miedema.[16]

Glycation of amino groups changes the physical and chemical properties of the proteins so that they can be separated from the nonglycated proteins by chromatographic or electrophoretic procedures (**Figure 2**). Hemoglobin A1c is the most prevalent glycated species, and glucose is the carbohydrate in it, whereas other carbohydrates, some of which still need to be established with certainty, constitute the other fractions.[14]

Physiological Relationship between Glucose and Hemoglobin

In addition to physiological parameters, such as temperature, pH, lifetime of protein, substrate concentrations, and individual influencing parameters, the rate of ketoamine formation is dependent on the reactivity of the amino groups. For the hemoglobin molecule, with 2α- and 2β-chains, the terminal amino group of the β-chain is preferred, giving the well-known HbA1c compound. Since erythrocytes are freely permeable to glucose, the rate of formation of GHb is directly proportional to the ambient glucose concentration in which the erythrocyte circulates to the duration of the exposure and the turnover of the erythrocytes.[18]

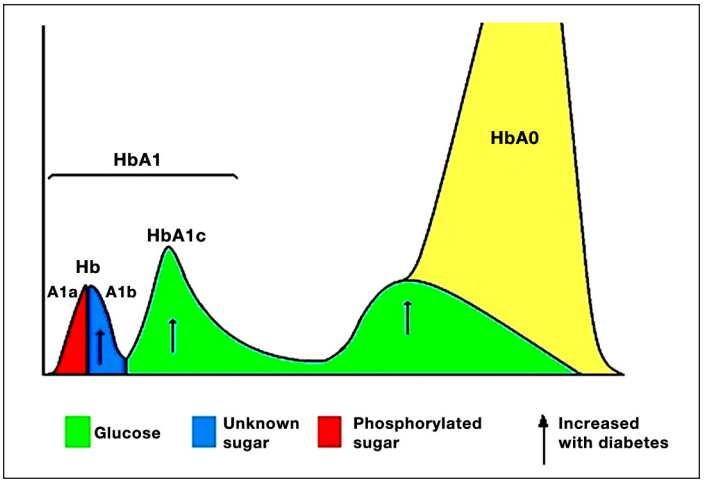

Figure 2. Separation of GHb species by ion exchange chromatography. Hemoglobin A1, which is more negatively charged than HbA0, can be further separated into its constituent parts HbA1a, HbA1b, and HbA1c, which are named in order of their elution from the column. Adapted from Fiedler and Zawta.[17]

These posttranslational modifications of the HbA molecule to form GHb are essentially irreversible, and glycation of hemoglobin occurs over the entire lifespan of the erythrocyte; the level of GHb is an integrated measure of the average blood glucose during these 120 days.[19–23] The question is, how accurate can this be? If the lifespan of the erythrocytes is normal, then the percentage of GHb is a reliable indicator for the glycemic state of a patient during the past 2–3 months, but not if the lifespan is reduced. Within these 120 days, recent glycemia has the largest influence on the HbA1c value. Theoretical models and clinical studies suggest that, in a patient in stable control, half of its HbA1c levels will be formed in the current month before the test, 25% in the month before that, and the remaining 25% in the months 2 to 4.[24,25]

Therefore, HbA1c is an integrated measure of glycemic variation that may consist of glucose excursions from hypoglycemia to normoglycemia to fasting and postprandial hyperglycemia.

A large number of medical conditions are associated with alterations in the relationship between MBG and HbA1c. Hematological conditions such as the presence of hemoglobin variants, iron deficiency, and hemolytic anemia, the presence of carbamylated hemoglobin in uremia, a variety of systemic conditions, including certain forms of dyslipidemia, malignancies, and liver cirrhosis, various medications, and finally, pregnancy are among the factors that influence the HbA1c measurement and, as a consequence, the MBG/HbA1c relationship.[26,27]

When an abnormal hemoglobin is present in the blood (such as HbS, HbC, HbE, or HbD), it is glycated either in addition to or instead of HbA1c. Modern glycohemoglobin analyzers can identify the nonglycated portion of these abnormal hemoglobins (but not the glycated portion). Nevertheless (even with such knowledge), it is very difficult to estimate what the HbA1c would be if the hemoglobinopathy was not present. This is even more difficult in patients who have homozygous hemoglobinopathies where there is no HbA present at all. Some analyzers that base their analysis on affinity chromatography can more easily identify glycation on any form of hemoglobin molecule, as can immunoassay methods, but even then, there is evidence that some abnormal hemoglobins glycated at rate compared with HbA and so may give rise to misleading results.[28–38] A detailed review (and references) on the effect of various hemoglobin variants on HbA1c results according to commercial method of measurement can be found on the National Glycohemoglobin Standardization Program Web site (*http://www.ngsp.org/factors.asp*).

The common condition of iron deficiency anemia can lead to rises in HbA1c levels of up to 2% that can be reversed by iron treatment.[39–43] The reason for this rise is not fully understood, and since iron deficiency is a common finding, especially in premenopausal women, it could influence not only the relationship between MBG and HbA1c, but also the management of these patients.[44] However, the overall relationship between mean plasma glucose (MPG) and HbA1c, in the population of premenopausal women participating in the DCCT, was similar to that of men, suggesting that overt anemia is required in order to have a significant effect on HbA1c measurement.[45]

On the other hand, hemolytic anemia as well as recovery from acute blood loss seem to have the opposite effect to iron deficiency by reducing HbA1c in affected individuals. Reports have shown that abnormally low HbA1c levels may be associated to conditions such as hereditary spherocytosis, elliptocytosis, autoimmune or drug-induced hemolytic anemia, and anemia due to chronic renal failure. These conditions are characterized by reduced red cell survival and therefore by a reduction in the availability of hemoglobin for glycation.[46–50]

Also, any drug that gives rise to hemolytic anemia will have the same effect. High-dose aspirin can also give spurious rises in HbA1c by forming acetylated hemoglobin, although not all methods are affected (see again National Glycohemoglobin Standardization Program Web site). Renal failure also has complex influence on HbA1c formation and measurement. These patients may exhibit hemolytic anemia, can be iron deficient, and have altered red cell survival. To add to these conditions, high levels of urea in the blood can lead to formation of carbamylated hemoglobin that can interfere with some methods of HbA1c measurement. However, carbamylated hemoglobin does not present an analytical interference in most modern methods of measurement.[51] Hyperglycemia itself is also responsible for shortened red cell lifespan, suggesting a mechanism by which mean glycemia may not exhibit a direct linear relationship to HbA1c levels.[52]

Pregnancy is also associated with a substantial reduction in HbA1c levels, and it has been consistently reported that pregnant women (with diabetes or not) have lower HbA1c levels than nonpregnant women.[53–55] However, controversial data exist about the last trimester of pregnancy, where some authors find elevations,[53,56,57] some decreases,[55,58] and some no difference among trimesters.[59] Explanations varied from iron deficiency (in order to explain HbA1c increase) to hemodilution and increased red cell turnover (in order to explain the decrease).

However, HbA1c levels do not give an indication of the stability of glycemic control. This is because, at least in theory, a patient with wide fluctuations in glucose concentrations could have the same HbA1c levels with another whose glucose levels vary little throughout the day.[24] Indeed, short changes in glucose concentration (for example, during an oral glucose tolerance test) or acute fluctuations, such as those that occur with illness or after meals, do not raise the concentration of the ketoamine compound, since the Amadori rearrangement occurs more slowly than the cleavage of the aldimine compound. Therefore, a normal HbA1c (i.e., 6%) can give a false sense of control when, in real life, blood glucose concentrations can fluctuate greatly.[60] As a result, HbA1c cannot represent the actual dynamics of glucose regulation. Other parameters are needed to assess better the role of glycemic variation in health and disease.

Little evidence has been available to establish whether two patients with the same MBG but very different glucose variability (GV) would have similar HbA1c values. However, two studies—one using DCCT data—have shown that glucose instability seems to have little influence on the HbA1c result. Rather, it is the mean glucose that appears to be the main determinant; not how that mean is achieved.[2,61]

An analysis of the A1c-Derived Average Glucose (ADAG) study database focused on measures of glycemia, such as GV, postprandial glycemia, MBG, and HbA1c and their association with cardiovascular risk factors.[62] Glycemic variability has been considered a HbA1c-independent risk factor for diabetic complications.[63–65] Although, in another analysis of the same population, they found that GV showed significant impact on the MPG–HbA1c relationship only in type 1 diabetes mellitus (T1DM) patients, leading patients with high GV to higher HbA1c levels for the same MPG;[66] they concluded that mean glycemia and HbA1c rather than postprandial or GV showed stronger, consistent associations with cardiovascular disease risk factors.[62] As many trials demonstrated, microvascular and macrovascular complications are mainly dependent on dysglycemia, which has two components: chronic sustained hyperglycemia and acute glycemic fluctuations from peaks to nadirs.[65,67–69] Both components lead to diabetic complications through two main mechanisms: excessive protein glycation and activation of oxidative stress. However, a study involving patients with T1DM failed to find a relation between high GV and levels of oxidative stress in these patients.[70] The explanation offered by the authors was that, unlike type 2 diabetes mellitus (T2DM) patients, T1DM patients are not sensitive to GV as a stimulator of oxidative stress because of different underlying pathophysiological mechanisms and the more accurate laboratory method (mass spectrometry) used to measure urinary excretion of prostaglandin, which gave lower results than in previous studies.

Variability of HbA1c measurements depends on both analytical and biological variation (BV). Biological variation has generally been defined as "random fluctuation around a homeostatic set point," and it is the sum of two components: intraindividual and interindividual BV.[71,72] Hemoglobin A1c is subject to BV and has been reported in individuals without diabetes,[73] where MBG has little impact on HbA1c levels. However, because HbA1c concentrations have been used for individual patient management, only analytical imprecision and intraindividual BV were considered relevant.[74]

Several studies have examined BV in individuals with diabetes and have concluded that there is a significant BV in HbA1c values that must be considered when interpreting test results.[61,74] It is important to note that, in patients with diabetes, fluctuations in HbA1c concentrations are not usually random but are mostly caused by changes in mean glycemia. In our opinion, it is not so clear how a homeostatic set point can be determined for an individual with diabetes, because this set point can (and often does) change over time.

However, although several studies have shown that intraindividual BV of HbA1c that is unrelated to glycemia is minimal, there is substantial interindividual BV also unrelated to glycemic status. Several investigators suggested the high- and low-glycator hypothesis. A high glycator has constantly higher HbA1c levels than expected for his MBG, whereas a low glycator has lower HbA1c than his MBG would suggest. Proposed explanations include interindividual differences in tissue glycation, factors influencing the membrane influx/egress of glucose or binding to hemoglobin, and finally genetic factors.

McCarter and colleagues,[75–77] analyzing their own data as well as DCCT data, proposed the use of a hemoglobin glycation index as a method to quantify BV. Hemoglobin glycation index is the difference between a patient's measured HbA1c and the predicted HbA1c. Predicted HbA1c was calculated from the patient's MBG using a multiple regression equation that compared HbA1c and MBG for the studied population.

Among individuals without diabetes, only approximately one-third of the variance in HbA1c is explained on the basis of measures of glycemia.[78] This observation suggests that other factors may be the cause of this variation in HbA1c levels. Some factors proposed to be associated with variation in HbA1c independent of glycemia are age, sex hormones, visceral fat distribution, other physiologic and genetic factors, and socioeconomic status, including racial and ethnic differences.[79–85]

Differences in HbA1c levels that cannot been explained by differences in glycemia have been described in several studies involving participants from different ethnic groups such as Hispanic whites, non-Hispanic blacks, Asians, and native Americans (see also a review by Herman[86]).[87–90] The reason for these racial differences remains to be established. It is also important to determine whether these differences among individuals or groups have an impact on complications or merely reflect variation in hemoglobin glycation.[86]

Twin and family studies have shown that HbA1c levels are heritable in nondiabetic individuals.[80,91,92] In addition, significant correlation in HbA1c between monozygotic twins both concordant and discordant for type 1 diabetes,[80,93] as well as in siblings with type 1 diabetes,[94,95] suggests that some genetic factors influence HbA1c in individuals with and without diabetes. Studies involving twins showed the substantial contribution of genetic influences to the variance in fasting blood glucose levels as well as in HbA1c levels.[92]

Correlations between HbA1c and fasting blood glucose were low, and genetic factors influencing HbA1c and fasting glucose were uncorrelated. These results suggest that, in healthy adults, the genes that influence fasting blood glucose and HbA1c reflect different aspects of glucose metabolism. Therefore, these two glycemic parameters cannot be used interchangeably in diagnostic procedures or in studies attempting to find genes for diabetes since they contribute unique information.[92]

Mathematical Relationship between Hemoglobin A1c and Mean Blood Glucose

We found seven studies comparing blood glucose levels at specific times of the day with HbA1c levels, showing that postprandial blood glucose values were more closely associated with HbA1c levels.[96–102] However, the strongest correlation was observed between HbA1c and MPG levels. Four cohort studies of patients with diabetes have compared overall MBG levels with HbA1c.[77,103–105] All but one[105] were limited to T1DM. Study periods ranged from 1–6 months and frequency of blood glucose measurement ranged from two to four times per day. Correlation coefficients between MBG levels and HbA1c ranged from 0.71 to 0.86, implying that 50% to 74% of the variance in HbA1c is explained by the MBG. But it was the study of Rohlfing and associates[99] that clearly documented that this relationship can be described by a simple linear regression equation (**Table 2**). The significance of this finding was that, knowing a patient's HbA1c, one could calculate MPG using an equation and therefore have an estimate of MBG levels for the previous 2–3 months. However, the major drawback of this study was that it was based on a retrospective examination of seven-point glucose measurements from T1DM patients during the DCCT. The DCCT was not designed to examine this relationship. Therefore, more prospective studies were needed to confirm this finding. Nevertheless, the impact of this relationship was considered sufficiently demonstrative to serve as a reference in the standards of medical care in diabetes that are published every year by the American Diabetes Association.[106]

There have been other studies (**Table 2**) that showed good correlation between MBG and HbA1c.[77,107,108] Makris and coworkers[107] reported results similar to that observed in the DCCT using patients with T2DM.

Hempe and colleagues[77] also reported a strong relationship, although they used HbA1c as independent variable. They also found significant differences in a large number of patients between the HbA1c measured result and the HbA1c that their MBG could predict. These differences were not related to erythrocyte age or analytical errors, and the concept of high and low glycators was introduced.

Calculation of MBG in those studies suffered either from portable meter inaccuracies or infrequent measurements

Table 2.
Summary of Published Studies Reporting a Relationship between Mean Blood Glucose and Hemoglobin A1c[a]

Source (first author)	Number of patients	Type of patients	Equation a = slope × b + intercept	R^2	Curve type	MBG increase per 1% HbA1c increase in mg/dl (95% confidence interval)
Hempe[77]	682	T1DM	HbA1c = 0.027 × MBG + 5.8[b]	[c]	linear	—
Rohlfing[99]	1439	T1DM	MBG = 36.6 × HbA1c -77.3	0.67	linear	35.6
Makris[107]	140	T2DM	MBG = 34.7 × HbA1c - 79.2	0.87	linear	34.7 (32.5–37.00)
Nathan[108]	15 7 3	T1DM T2DM Nondiabetic	MBG = 31.5 × HbA1c - 68.6	0.79	linear	31.5
DirecNet[111]	48	T1DM	MBG = 28.0 × HbA1c + 40.0	—	linear	18.0 (14.0–22.0)
ADAG[110]	268 159 80	T1DM T2DM Nondiabetic	MBG = 28.7 × HbA1c - 46.7	0.84	linear	28.7
JDRF-CGM[112]	252	T1DM	MBG = 24.4 × HbA1x - 16.2	0.63	linear	24.4 (22.0–26.7)

[a] An excellent review of the literature can also be found in Reference 55.
[b] HbA1c was used as independent variable.
[c] Pearson correlation coefficient r = 0.71 was reported by authors.

of blood glucose and HbA1c. Newer studies incorporated the use of continuous glucose monitoring (CGM) sensors together with SMBG. Four studies examined the MBG–HbA1c relationship using CGM sensors.[108–112] Two studies involved adults,[108,110] one children and adolescents,[111] and one mixed population[112] (**Table 2**).

Nathan and associates[108] suggested that translation of HbA1c to an average glucose level for reporting and management purposes was feasible. Their results were confirmed by the ADAG study,[110] where the authors concluded that, using their equation, HbA1c levels can be translated safely as estimated average glucose (eAG) for the majority of patients with T1DM or T2DM. On the other hand, the remaining studies[111,112] showed substantial variability in individual mean glucose concentrations for a given HbA1c, and therefore they concluded that trying to transform HbA1c into calculated mean glucose might introduce substantial error.

Borg and coworkers,[113] further analyzing ADAG study data, examined the relationship among common indices of postprandial glycemia, overall hyperglycemia, GV, and HbA1c. They found that, although fasting blood glucose is not a clear indicator of general glycemia and not a single blood glucose measurement during the day can accurately predict the HbA1c value of the patient, it is the preprandial glucose values that have the largest impact on HbA1c levels rather than the postprandial values, presumably because they resemble the 24 h glucose levels (and thus the long-term exposure to glucose) more closely.

There is very limited information of how much time nondiabetic individuals spend at different levels of glycemia under real-life conditions, because studies that have involved healthy individuals incorporated a very limited number of measurements. Borg and coworkers[114] studied the profiles of healthy individuals that participated in the ADAG study in order to identify the extent in which healthy individuals exceed oral glucose tolerance test thresholds for impaired glucose tolerance and diabetes. Nondiabetic individuals were selected on the basis of having no history of diabetes, a fasting blood glucose <5.4 mmol/liter (97 mg/dl), and HbA1c <6.5%. They found that 10% of these patients spent a considerable amount of time of their follow-up at glucose levels considered to be prediabetic or indicating impaired glucose tolerance. This shows that current classification of individuals based on isolated glucose measurements may underestimate exposure to moderately elevated glucose levels.

Conclusions

The biochemistry of glycation predicts a close relationship between HbA1c and MBG. The clinical studies reviewed here verify this close relationship with correlation coefficients varying from 61% to 93%. Although impressive from a statistical point of view, these associations cannot explain a substantial (and sometimes clinically important) part of HbA1c variance (approximately 75% of its variance can be attributed to MBG). The prediction intervals of regression equations are rather wide, giving a not-so-accurate translation of HbA1c to MBG and the opposite. It is evident that, in this equation, other parameters should be taken into account if we want a "one-size-fits-all" equation. Biological variation seems to have a role in this relationship and has to be taken into account when we try to establish this relationship, but no proposed equation has incorporated it.

This is not the only problem in this relationship. Apart from the pathological and physiological conditions that cannot be quantified easily (as BV) and that affect the relationship, when trying to establish a mathematical equation between two biological quantities, there are problems not only in determining the type of mathematical equation that will best describe their relationship, but also the accuracy of how these two quantities are measured or calculated. In our case, we placed at the right side of the equation a directly measured biomarker (HbA1c) and on the left side a biomarker that is calculated from multiple measurements over time.

Analytical requirements for HbA1c are different when the test is used for monitoring glycemic control, where reproducibility is important and different when it is used to calculate MBG. In the latter case, errors in measurement may produce unexpectedly large changes in estimated MBG. The issues of global standardization of HbA1c measurements were successfully confronted by the International Federation of Clinical Chemistry with the development of an internationally accepted reference system.[115,116] Clinical laboratories use methods and analyzers that are traceable to this reference, although many diabetes centers and private practice physicians rely on point-of-care instruments to measure HbA1c, with some of them not showing acceptable analytical performance.[117,118]

The second problem is the calculation of MBG from patient self-monitoring. This can be achieved today either by portable meters or CGM or combination of the two.

Screening by portable meters, although attractive because of convenience and accessibility, is not as accurate as measuring blood glucose in a clinical laboratory[64,119,120] (**Table 3**). Discrete glucose measurements obtained over the day often fail to capture the true magnitude of glycemic excursions commonly found in patients with T1DM and underestimate the extent and frequency of nocturnal hypoglycemia.[65,121] The use of CGM sensors may solve the problem of infrequent measurements, but this introduces other issues that affect their accuracy (the interstitial glucose level estimated by these instruments may not technically be identical to the blood glucose level), calibration, and long-term performance.[122]

In conclusion,

- most studies today have confirmed a close relationship between HbA1c and MBG, although different studies result in different equations;
- wide prediction intervals in these equations corrupt for the moment an accurate conversion of HbA1c to eAG;
- although eAG can be used as education by the physician to explain the meaning of HbA1c to a patient, it should not be reported as a result by laboratories for the time being;
- more studies are needed that will address the previously mentioned limitations (e.g., BV, analytical issues of SMBG) if we want a unique equation to describe this close relationship;
- HbA1c and SMBG provide different information on patients, and they should be used as such; and finally,
- although all studies propose a linear equation to describe this relationship, sometimes (see Reference 54, **Figure 1**) data seem to follow a nonlinear pattern, which serves as a reminder that the world we live in is not linear.[123]

Table 3.
Factors Affecting Accuracy in Portable Glucose Meters[62–64]

Type of error	Effect on result
Operator-related errors	variable
Improper use of control solutions	variable, introduction of systematic error
Improper maintenance of portable meters	variable
Poor hand wash	variable
Improper storage of strips	variable
Less reliable at low glucose concentrations	variable
Overestimate hyperglycemia	elevated
Affected by certain drugs, i.e., ascorbic acid acetaminophen dopamine mannitol	variable depends on the methodology the meter uses
Hematocrit anemia polycythemia	 elevated lower
Alternative site of testing	may give elevated postprandial results and lower after exercise
Hypothermia	elevated
Hypotension	elevated

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