The Challenge of the Use of Glycemic Biomarkers in Diabetes: Reflecting on Hemoglobin A1C, 1,5-Anhydroglucitol, and the Glycated Proteins Fructosamine and Glycated Albumin

Lorena Alarcon-Casas Wright, MD, and Irl B. Hirsch, MD

Frequent evaluation, as well as precise measurement, of glycemic control is a crucial part of optimal care for patients with diabetes. Glycemic biomarkers are important tools used to determine whether a patient’s metabolic control has been maintained within the target range, but most importantly, they are used as surrogates to estimate and reduce the risk of chronic diabetes complications. Below, we review clinical instances in which A1C should not be used and reflect on the use of other glycemic biomarkers that can be used in substitution, as well as their individual limitations.

Hemoglobin A1C
In 1969, an increase in an “unusual” hemoglobin was first observed in patients with diabetes. It was later learned that, in red blood cells (RBCs), glucose binds to the α-amino position of hemoglobin β-chains (valine) in an aldime or Schiff base linkage, and this process could partially rearrange in a reversible manner to form a ketoamine linkage, resulting in a “glycated” hemoglobin, or hemoglobin A1C. In 1976, it was reported that A1C reflects the mean blood glucose concentration over previous weeks to months and that its periodic monitoring could provide a useful way of documenting glycemic control.

Currently, A1C is a widely used glycemic marker and is considered by the American Diabetes Association, along with self-monitoring of blood glucose (SMBG), as the primary technique to assess glycemic control. It provides information about the degree of glucose control during the previous 8–12 weeks in the nonpregnant population. A1C has been used as a primary treatment target for diabetes because of the large intervention studies in both type 1 and type 2 diabetes associating improved glycemic control with a decreased risk of microvascular disease.

It should be noted that early use of A1C in these two landmark studies could not be extrapolated to others because of the lack of assay standardization of A1C. Currently, the National Glycohemoglobin Standardization Program (NGSP) has decreased potential technical errors, and standardization is close to universal.

However, in addition to the importance of standardization, it is also important to be aware of other clinical situations in which A1C may not be an accurate reflection of glycemic control in diabetes.

Average Glycemia Versus Glycemic Variability
Exposure to dysglycemia in diabetes can be simplified as a function of several components, including the duration and severity of chronic hyperglycemia and the acute fluctuations of glucose over a time period. A1C in a patient with a normal hematological profile is the reflection of that patient’s average glucose control during the previous 2–3 months; as such, A1C is mainly a reflection of the
first component of dysglycemia, with contributions from postprandial and fasting hyperglycemia.\textsuperscript{8,9}

Recent studies in vitro\textsuperscript{10–12} and in humans\textsuperscript{13,14} strongly suggest a second component, namely, the acute excursions of glucose around a mean value (i.e., hyperglycemic glucose fluctuations but also hypoglycemic exposure around mean glucose) described as “glycemic variability.” Glycemic variability may be a significant risk factor for microvascular complications, along with A1C and genetics, and it may help to explain why some patients develop microvascular complications and others having the same A1C do not. In a study involving patients with either type 1 or type 2 diabetes using continuous glucose monitoring (CGM), the standard deviation (SD; a measure of variability) had no impact on A1C in type 2 diabetic patients but did influence A1C in type 1 diabetic patients.\textsuperscript{15}

It is therefore important to be aware that A1C in general is a crude marker of dysglycemia. It is also important to note that postprandial hyperglycemia does not necessarily equate to glycemic variability; instead, postprandial hyperglycemia should be regarded as a component of glycemic variability.\textsuperscript{16}

As a result of the development of outpatient CGM capabilities, glycemic variability is being studied and targeted more aggressively. But, as of now, there is no definitive proof that improving glycemic variability can change the natural history of diabetic vascular disease. One problem is that there is not a perfect serum biomarker of glycemic variability.

A1C: Sources of Misinterpretation

1. RBC lifespan
RBCs are freely permeable to glucose. As a result, glucose enters the cells and attaches to hemoglobin at a rate dependent on the serum blood glucose. Hence, A1C glycation is dynamic and depends not only on average glycemia but also in the rate of production (and destruction) of RBCs. Conditions that affect RBC lifespan will invariably have an impact on A1C results.

RBCs that have a short lifespan secondary to destruction (i.e., hemolytic anemia,\textsuperscript{17} destruction through the passage of abnormal heart valves,\textsuperscript{18} or splenomegaly) will result in a low A1C independent of the mean serum glucose. This situation is also present in circumstances in which the bone marrow increases the production of young RBCs (reticulocytes), as seen in patients with chronic kidney disease (CKD) who receive erythropoietin treatment for anemia; post-hemorrhage, as the healthy bone marrow is stimulated by hypoxia; or after a blood transfusion.\textsuperscript{19} A1C values have been found to be positively associated with hemoglobin concentrations and negatively associated with erythropoietin dose.\textsuperscript{20} In addition to erythropoietin, medications that affect RBC mass, such as dapsone,\textsuperscript{21} will affect A1C results.

The falsely lowered A1C may lead to the wrong assumption of adequate glycemic control. Table 1 summarizes sources of misinterpretation for A1C and other glycemic biomarkers.

2. Presence of hemoglobinopathies
Hemoglobinopathies such as sickle cell traits (hemoglobin S) and other abnormal hemoglobin variants such as hemoglobin C and E can lead to falsely high or low A1C readings depending on the laboratory methodology used.\textsuperscript{22–24} Comprehensive information regarding A1C assay interferences in patients with hemoglobinopathies is found at the NGSP Web site.\textsuperscript{7}

3. Iron status
Previous studies suggest that iron deficiency with\textsuperscript{25} and without\textsuperscript{25,26} anemia affect the level of A1C independent of glycemia. Iron is important for hemoglobin synthesis and RBC production. In negative iron balance status, the iron and hemoglobin deficiencies are followed by deficient RBC production, translating to a slow turnover of RBCs and mostly “mature” cells circulating in the bloodstream, allowing more time for glycation and falsely increasing the values of A1C.

| Table 1. The Most Common Sources of Error in the Interpretation of Glycemic Biomarkers |
|--------------------------------------------------|-------------------------|-------------------------|-------------------------|
| Sources of Error                                 | A1C                     | Glycated Proteins       | 1,5-AG                  |
| Mechanism                                        | Conditions or treatments that alter RBC half-life | Conditions or treatments that alter protein metabolism | Conditions or treatments that alter renal function or threshold for glucose |
| Falsely High Values                              | • Iron deficiency       | • Hypothyroidism        | • CKD stage 4–5          |
|                                                 | • Anemia                | • Cirrhosis of the liver|                         |
|                                                 | • Hemoglobinopathies    |                         |                         |
|                                                 | • Race: African American, Hispanic, Asian |                         |                         |
| Falsely Low Values                               | • Hemolysis             | • Hypoalbuminemia:      | • Pregnancy             |
|                                                 | • Reticulocytosis       | protein-losing enteropathy, nephrotic syndrome, liver failure |                         |
|                                                 | • Hemoglobinopathies    | • Hyperthyroidism       | • Chronic liver disease |
|                                                 | • Post-hemorrhage or    | • Hyperuricemia         | • Glucokinase–maturity-onset diabetes of the young |
|                                                 | post-transfusion        | • Hypertriglyceridemia  |                         |
|                                                 | • Drugs: iron, erythropoietin, dapsone | • Nonalcoholic fatty liver disease |                         |
|                                                 | • Uremia                |                         |                         |
|                                                 | • Splenomegaly          |                         |                         |
Data from the National Health and Nutrition Examination Survey 1999–
2006\(^{27}\) found that iron deficiency was, not surprisingly, more common
in women than in men and that this iron deficiency was not necessarily
accompanied by anemia. Among women, 13.7% had iron deficiency, and
30% of iron-deficient women had anemia. Iron deficiency is much less
common in men; 1.6% had iron deficiency, and 33% of iron-deficient
men had anemia. In this representative healthy, adult, American population
sample, it was found that iron deficiency shifted A1C slightly upward at
the lower end of the A1C spectrum independent of fasting glucose level.\(^{27}\)
These observations were also reported in other studies involving people with
iron deficiency anemia presenting with higher A1C values relative to plasma
glucose levels.

Conversely, correction of iron deficiency with oral iron results in
a decrease of pretreatment levels of A1C.\(^{26,28}\) In one of the studies in people
without diabetes, A1C decreased significantly after iron treatment from
a mean of 7.4 ± 0.8 to 6.2 ± 0.6% (\(P < 0.001\)).\(^{26}\)

Recently, a study in India\(^{29}\) of 116 young adults with different degrees of
blood glucose tolerance, as characterized by an oral glucose tolerance test (OGTT),
showed that the sole use of A1C to diagnose diabetes or pre-diabetes
may spuriously elevate its prevalence, independent of glycemic tolerance, as
significantly influenced by iron status. Based on these observations, iron
deficiency with and without anemia must be ruled out or corrected before
any diagnostic or therapeutic decision is made based solely on A1C. Table 2
summarizes the effect of iron treatment on A1C values in people with
and without diabetes.

4. **Racial differences**

Several epidemiological studies have found higher A1C values in minority
groups, mainly African Americans, across different degrees of glucose tol-
erance status\(^{30,31}\) and independent of glycemic control.\(^{32}\) When adjusted for
variables such as age, sex, duration of diabetes, and glucose tolerance sta-
tus among many others, A1C values remained higher. Several hypotheses
have been proposed, including differences in the RBC permeability to
Glucose, differences in 2,3-diphospho-
glycerate (responsible for the rate of
production of A1C),\(^{33}\) and differences
in RBC membrane gradients.\(^{34}\)

Recently, a cross-sectional study
in African-American and white people
with and without diabetes was conducted to investigate
such racial disparities in A1C and included glycemic biomarkers that
would be unaffected by hemoglobin
glycation and erythrocyte turnover
(fructosamine and 1,5-anhydroglu-
citol [1,5-AG]).\(^{35}\) The results were in
agreement with previous studies that
A1C is higher in African-American
people; however, they also had sig-
ificantly higher values of other
glycated proteins compared to white
people before and after adjustment
covariates and fasting glucose. Serum 1,5-AG was lower in African
Americans compared to white peo-
ple, although this was statistically
significant only in the non-diabetic
adult cohort. The results of this study
suggest that such discrepancies may
actually not be completely indepen-
dent of glycemia.\(^{35}\) Nonetheless, the
etiology of such differences remains
poorly understood.

**A1C in Patients With CKD**

A common clinical challenge in assessing
glycemic control is encountered in patients with diabetes and CKD. Not
infrequently and depending on the degree of renal impairment, patients
with CKD present with anemia of multifactoral etiology; erythropoietin
deficiency, decrease in RBC survival, decreased response of marrow pre-
cursor cells to erythropoiesis signals, and iron deficiency are among the
causes.\(^{36,37}\)

Uremia has been proposed as a key
factor in the short lifespan of RBCs
of patients undergoing hemodialysis,
possibly secondary to an increase in
osmotic and mechanical fragility of
RBCs; however, the mechanisms are
still unclear.\(^{37}\) The uremic state also
affects the accuracy of the A1C assay
due to glucose or differences in
2,3-diphosphoglycerate would not be
expected to affect their glycation rate.

1. **Fructosamine**

Fructosamine refers to the measure-
ment of total serum proteins that have
become stable irreversible ketoamines,
with GA accounting for ~ 90%. Serum
proteins have a shorter half-life (15–20
days) than A1C, providing an index of
glucose control over a period of 2–3
weeks.

There are clinical situations in
which fructosamine should not be
used. Abnormal protein turnover
influences fructosamine values, as
in thyroid disease (i.e., in thyrotoxic
and hypothyroid patients, in whom
protein turnover is increased and
decreased, respectively).\(^{40}\) Values
are also influenced by low concentrations
of albumin and plasma proteins, as in
cases of protein-losing enteropathy,
nephrotic syndrome, or liver failure
and by low-molecular-weight sub-
stances such as urea, uric acid, and
bilirubin.\(^{42}\)

Clinicians must exercise caution
when interpreting fructosamine
results in patients with an abnormal
rate of serum protein turnover. Van Dieijen-Visser et al. were the first to confirm that the fructosamine concentration depends on the concentration of serum albumin and suggested that the values be corrected by subtracting 0.023 mmol fructosamine for every gram of albumin per liter. Subsequently, a study that considered estimated average analytical variance and intra-individual variance proposed the following formula: corrected fructosamine (mmol/l) = [measured fructosamine + 0.03 (40 – serum albumin g/l)], mmol/l.

Because it is uncertain which correction or formula is best for use in clinical practice, we recommend ensuring that the patient has a normal albumin level when deciding to use fructosamine as a marker of glycemic control. The need to correct or adjust to albumin levels is clearly a limitation to the use of this glycemic biomarker. Given the glomerular lesion of diabetic kidney disease, fructosamine levels may have limitations in this population.

2. Glycated albumin
GA has been studied mainly in the nephrology field. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population. Several studies have shown its superiority compared to A1C in patients with CKD stage 4–5 who are undergoing hemodialysis. In patients with advanced CKD, GA has been studied mainly in the population.
and the risk of progressing nephropathy. Conversely, a negative GG was described in the group of subjects with no nephropathy or with a lower risk of progression. Furthermore, in subjects with type 2 diabetes, the GG predicted the progression of nephropathy, even after adjustment for A1C.

The GG has also been associated with the risk of developing retinopathy in a study that included 84 type 1 diabetic patients followed for complications over 4–14 years. A1C, fructosamine, and random glucose measured at the 4-year exam were significantly higher in those who subsequently developed retinopathy than in those who did not. Fifty percent of the patients developed retinopathy at 9 years, and a significant difference in the GG was found between those with and without subsequent retinopathy, being positive in those with retinopathy and negative in those without.

Further studies are needed to investigate the physiology behind the differences in glycation processes in the different compartments and their influence and correlation with diabetes complications. The identification of such processes affecting glycation not only may have bearing on the use of glycemic markers, but also may help determine, alleviate, or prevent the rate of development of diabetes-related complications.

1,5-AG

1,5-AG was first discovered in the plant family Polygala senega in 1888. The structure was identified in 1943, and the presence of the compound in human blood was established in 1973. 1,5-AG has been clinically used in Japan for more than a decade to monitor short-term glycemic control. It originates mostly from foods, with the dietary intake closely matched by the daily excretion rate and a small percentage originating from de novo biosynthesis. 1,5-AG is well absorbed in the intestine and distributes to all organs and tissues. Dietary variation of this compound was not found to affect the efficacy of 1,5-AG as a marker of glycemic control. However, this has only been assessed in Japanese patients and not in other populations with different dietary habits.

In a healthy cohort, 1,5-AG varied widely (12–40 mg/ml), with mean values in males significantly higher than in females. In the pediatric population, males were also found to have higher 1,5-AG levels than females, and this included patients (4.5 ± 2.3 vs. 3.4 ± 1.6 μg/ml, P = 0.003) and controls (26.0 ± 6.6 vs. 23.5 ± 6.0 μg/ml, P = 0.02).

When serum glucose is high in diabetic patients, glucose prevents 1,5-AG reabsorption in the renal tubules, leading to its excretion in the urine and thus decreasing levels in serum. It has also been shown that, after achieving better glycemic control in previously hyperglycemic patients, levels of 1,5-AG increase, indicating that decreased levels are reversible once glucose control is improved.

1,5-AG is a reflection of glycemic control over the previous 48 hours to 2 weeks and may provide unique information beyond that provided by A1C, particularly in patients in whom A1C is <8%. In such patients with close-to-optimal A1C, 1,5-AG is a powerful predictor of postprandial hyperglycemia because it measures glucose excursions. As such, a lower level of 1,5-AG may be helpful as a complementary tool in the fine-tuning of glucose control.

Clinicians should be cautious when evaluating levels in patients whose renal function or renal threshold to glucose are different from normal (i.e., individuals with CKD or tubular defects) during pregnancy complicated by diabetes, in glucokinase–maturity-onset diabetes of the young, and in chronic liver disease. A recent study in 269 patients with type 2 diabetes and different stages of renal dysfunction found that 1,5-AG may be useful as a glycemic marker in individuals with mild to moderate kidney dysfunction, with stage 1–2 corresponding to an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m²; potentially in stage 3 CKD, with eGFR < 60 ml/min/1.73 m²; but not in individuals with advanced renal failure stage 4–5, with eGFR < 30 ml/min/1.73 m². Finally, 1,5-AG has not been adequately studied in patients with significant hyperglycemia and marked glycosuria (A1C > 10%).

Pregnancy Complicated by Diabetes

A1C is widely used in the management of pregnant diabetic patients, and, in combination with SMBG, it is considered the main tool to guide treatment, with the goal of decreasing the risk of complications in infants of diabetic women. In this specific population, A1C reflects the previous 6–8 weeks of average glycemia (versus 8–12 weeks in the nonpregnant population) because of the mean age of the RBCs and increased erythropoiesis during pregnancy.

In a study that included 24 women with diabetes first diagnosed during pregnancy, with a mean baseline A1C of 8.8 ± 1.8%, followed during the first 1–4 weeks of treatment to achieve normoglycemia, a decrease in A1C at a rate of 0.5% per week was demonstrated. It is unknown whether iron supplementation played a role in such rapid A1C decline; nonetheless, in this population, in which close follow-up is important, adequate treatment to achieve normoglycemia, guided by frequent point-of-care A1C monitoring throughout pregnancy, is a reasonable recommendation.

Other glycemic markers such as GA and fructosamine have not been studied as extensively as A1C. One study in a Japanese cohort of pregnant patients with diabetes reported that A1C levels were elevated in late pregnancy because of iron deficiency, but that GA was not affected, underscoring the importance of iron status on the correct interpretation of A1C, particularly in this population at risk for iron deficiency.

The literature on 1,5-AG during pregnancy is limited. Levels of 1,5-AG decrease during normal gestation in the presence of detectable glycosuria, secondary to changes in the renal threshold to glucose during pregnancy, confirming that 1,5-AG levels in pregnant women are low independently of serum glucose. SMBG continues to be the cornerstone of hyperglycemia management during pregnancy, and it should be considered an empowering tool for patients and their doctors to decrease fetal and maternal complications.

Case Presentations

Case study 1

A 52-year-old white woman with type 2 diabetes receiving insulin glargine and three oral agents has A1C levels consistently in the range of 7.4–7.8%. Her glucose meter average (on the meter itself) with three tests/day is usually in the range of 220–240 mg/dl. She has no anemia; iron studies and reticulocyte count are normal; and she has normal renal and liver function.
Because of the discrepancy between her SMBG average and her A1C, a fructosamine level was measured. Several days later, results showed her fructosamine was 399 µmol (normal < 285 µmol). What does this mean and how should this patient be managed and monitored?

**Case study 2**

A 64-year-old man with type 2 diabetes comes in for his first visit after an aortic valve replacement (AVR) 3 months earlier. His A1C levels have usually been in the 7.5–8% range, and his A1C is now 6.2%. His SMBG average, checking 3–4 times daily, is 177 mg/dl, with an SD of 62 mg/dl. It is decided to measure fructosamine and 1,5-AG levels, which are 235 µmol (normal < 285 µmol) and 11.5 µg/ml (normal > 10 µg/ml), respectively. He has nephrotic-range proteinuria, with a serum creatinine of 2.9 mg/dl (eGFR 26 ml/min). How should this patient be monitored?

**Case study 3**

A 24-year-old Hispanic woman is referred to the clinic for management of gestational diabetes mellitus (GDM). She was initially seen by her obstetrician the previous week at gestational week 12, and a screening 75-g OGTT showed the following results: fasting glucose: 100 mg/dl, 1- and 2-hour glucose levels: 184 and 159 mg/dl, respectively. An initial A1C at that time was 5.6%. She was prescribed prenatal vitamins.

Today at the clinic, she is asymptomatic and tells you that, secondary to her new diagnosis of GDM, she has started walking daily and avoiding carbohydrates. A fasting glucose measurement by point-of-care meter is 94 mg/dl, and her A1C is 5.2%. What are your recommendations?

**Cases Recommendations**

**Case study 1**

This patient has a negative GG, meaning that her measured A1C is lower than predicted by fructosamine and also discordant with results of her average SMBG. To prevent diabetes-related complications, her hyperglycemia should be treated aggressively with the addition of prandial insulin. Glycemic control should be monitored using fructosamine rather than A1C. She should also continue frequent SMBG, particularly when on an intensive insulin regimen.

**Case study 2**

With increasing comorbidities more often seen in aging patients, traditional biomarkers will not reflect glycemic control accurately. In this case:

- **A1C is not accurate because of AVR and CKD.**
- **Fructosamine is not accurate because of proteinuria and subsequent hypoaalbuminuria.**
- **1,5-AG is not accurate because of CKD stage 4–5.**

Solution: Monitoring glycemic control in this case will be dependent on SMBG results.

**Case study 3**

The patient has three of three abnormal glucose values during a 75-g OGTT. (Only one is needed for the diagnosis of GDM.) There are no clear guidelines for the frequency of A1C testing during pregnancy. In this situation and at this point in time, no conclusions can be made based solely on the A1C results or trend because:

- **A1C is lower during pregnancy than in the nonpregnant state.**
- **It is a standard of care to initiate prenatal vitamins with iron during pregnancy.** Correction of iron deficiency will concomitantly result in lower A1C values. This possibility cannot be ruled out in this patient, and we should not assume the trend of her A1C was solely secondary to lifestyle modifications.

Solution: Intensive SMBG is the cornerstone of glycemic control in pregnancy complicated by diabetes. Once iron stores have been repleted, A1C can be used as a glucose-control biomarker when the result is compared to the woman’s previous value, but only in conjunction with SMBG. Then, the rate of change of A1C (increase or decrease) may be of clinical utility.

**Conclusions**

All currently available glycemic biomarkers have advantages and limitations. It is unclear which marker or combination of markers may have the best relationship to complications for different populations of patients. Clinicians taking care of patients with diabetes should become familiar with the individual nuances of such biomarkers and identify one or a combination of them that can best translate accurate glycemic control. Similarly, clinicians should be able to identify situations in which glycemic markers are unreliable, by taking into consideration the period examined, comorbidities, and medications used by the patient.

When using A1C as a diagnostic tool for diabetes and pre-diabetes and before any diagnostic or therapeutic decision is made based solely on A1C, we recommend ensuring a normal hematological profile and normal iron status. We advocate for SMBG values and averages to be routinely compared to the elected glycemic biomarker(s). The frequency of SMBG will depend on the need for insulin therapy, presence of complications and comorbidities, and treatment regimen (insulin, oral hypoglycemic agents, or diet/exercise) to corroborate concordance to results of serum glycemic marker(s). If a glycation gap is discovered, fructosamine should be preferred over A1C.

SMBG becomes more crucial as we learn more about the different glycemic biomarkers and how they can complement each other. Finally, further research is needed to correlate the different glycemic biomarkers with diabetes-related complications.

**References**

association with prosthetic heart valves: a study of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 26:881–885, 2003


Hardikar PS, Joshi SM, Bhar DS, Raut DA, Katre PA, Lubrec HG, Jere A, Pandit AN, Fall CH, Yajnik CS: Spurious high prevalence of prediabetes diagnosed by HbA1c in young Indians partly explained by hematological factors and iron deficiency anaemia. Diabetes Care 35:797–802, 2012


Kim WJ, Park CY, Lee KB, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW: Serum 1,5-anhydroglucitol concentrations are a reliable index of glycemic control in type 2 diabetes with mild or moderate renal dysfunction. Diabetes Care 35:281–286, 2012


Lorena Alarcon-Casas Wright, MD, is a senior clinical research fellow in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington and at the VA Puget Sound Health Care System in Seattle. Irl B. Hirsch, MD, is a professor of medicine in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington in Seattle.