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Review Article

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Alternative Biomarkers for Assessing Glycemic Control for the Prognosis and Management of Diabetes

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Diabetes refers to a group of metabolic dysfunctions of multiple etiology marked by chronic hyperglycemia. The frequent evaluation and accurate measurement of glycemic control are cornerstones in the reduction of long-term diabetic complications. Glycemic biomarkers are essential tools used to determine whether a patient with diabetes has achieved glycemic control and maintained it within the target range; notably, they also act as surrogate biomarkers to estimate and reduce the risk of long-term diabetic complications. Although fasting plasma glucose, 2-h postprandial plasma glucose, and random plasma glucose provide information on glycemic control for diabetic diagnosis and management, they do not reflect glycemic control over a period of time. Traditionally, glycated hemoglobin (HbA1c) has been used as the gold standard glycemic control biomarker for long-term glucose monitoring. However, growing evidence indicates that HbA1c is not a suitable indictor as a result of various biological confounders and analytical interferences that limit its accuracy in reflecting true glycemia. Therefore, the use of glycated albumin, fructosamine, and 1,5-anhydroglucitol as well as a continuous glucose monitoring system may complement traditional measures, particularly in circumstances in which the measurement of HbA1c could be unreliable or biased in assessing the risk of diabetic complications. In this review, the suitability of blood glycated proteins as indices of long-term glycemic control was investigated and the selection of the appropriate glycemic biomarkers was outlined based on the clinical status of patients with diabetes. Valuable and useful point-of-care monitoring procedures were provided for the management of diabetes and the prevention of related complications.

Key words: glycemic biomarker, glycemic control, diabetic complications, glycemic variability, prognosis

Introduction

The ultimate goal of diabetes management is to attain and maintain stable glycemic

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control, decrease mortality, and prevent or delay the development of diabetic complications.[1] The Diabetes Control and Complications Trial (DCCT) supported the use of intensive glycemic control to delay the onset and reduce the development of diabetic complications in type 1 diabetes (T1D).[2] The Epidemiology of Diabetes Interventions and Complications study was an observational cohort study that demonstrated that maintaining glycemia as close to the nondiabetic range as safely possible reduced both micro- and macrovascular complications for 30 years in patients with T1D.[3] The results of the United Kingdom Prospective Diabetes Study (UKPDS) and its follow-up trials provided evidence of the beneficial effect of intensive glycemic control, reporting a reduction of the risk of diabetic complications and mortality in patients with type 2 diabetes (T2D).[4,5] Similar benefits emerged from the Veterans Affairs Diabetes Trial[6] and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial;[7] however, the risk of overall mortality was increased[8] likely as a result of the severe hypoglycemia side-effect of aggressive antihyperglycemic therapy.[9] These studies indicated that individualized glycemic control measured using clinically validated biomarkers rather than a one-size-fits-all approach may provide a valid rationale for optimal diabetes care.

Glycemic biomarkers are indispensable in clinical practice to guide therapy and assess medication efficacy on glycemic control. Traditionally, the concept of glycemic control is based on the self-monitoring of blood glucose (SMBG) along with laboratory testing for glycated hemoglobin (HbA1c), which is a surrogate biomolecule of the average blood glucose (BG) levels over the preceding 2 to 3 months.[10] HbA1c predicted the risk of diabetic complications and emerged as the optimal indicator of glycemic control in both the DCCT and the UKPDS trials and is widely used as the standard measure for diabetes care in contemporary clinical practice.[11] HbA1c not only provides valuable information on chronic hyperglycemia but also predicts the risk of the development and progression of diabetes complications.[12] However, biological and analytical studies, as well as some medical conditions, reduce its accuracy in reflecting the true glycemia level.[13] HbA1c functions as an indicator of overall glucose exposure through the integration of fasting, preprandial, and postprandial hyperglycemia; however, the relative contribution of each varies with the quality of glycemic control.[14] Hemoglobin (Hb) disorders may reduce indicator validity, and HbA1c neither provides information on glucose dynamics nor captures day-to-day changes in glucose concentrations.

These limitations of the HbA1c assay have led to investigations into an expanding group of alternative glycemic biomarkers that provide reliable information on short- and intermediate-term glycemic control, thus improving the quality of diabetes care and reducing the risk of diabetic complications across a heterogeneous population. In this review, point-of-care monitoring procedures are provided using different glycemic control biomarkers for optimizing diabetes management, with particular emphasis on the necessity of an individualized approach in utilizing and interpreting different tests in a manner aligned with the clinic.

Glycemic control biomarkers

The stringent assessment of glycemia is an essential component of diabetes care. Glycemic biomarkers are indispensable in clinical practice to guide therapy and investigate the efficacy of medications; they enable glycemic control in patients with diabetes within a set range and assist in reducing the risk of diabetic complications.[15] The characteristics of glycemic biomarkers are summarized in Table 1. These biomarkers not only present different timeframes for glycemic control but

also provide information on diabetic metabolism that may reflect different pathways.

Glucose

Glucose is a monosaccharide and the main metabolite of carbohydrate for energy production in the body. Therefore, the consumption of carbohydrate-rich foods results in variable and transient increases in postprandial BG concentrations, which can serve as a primary indicator of diabetes. Patients with diabetes are typically exposed to higher BG concentrations during fasting and postprandial glucose excursions, both of which represent key biomarkers for the diagnosis and treatment of the disease.[16] Both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) provide an acute assessment of glycemia and are therefore useful for monitoring the effects of diet, physical activity, and antidiabetic medications. The relative contribution of these measures change and cause increased HbA1c values.[14]

The relationships of FPG and 2-h PPG with mortality has been examined in several studies. The risk of mortality doubled when FPG levels exceeded 126 mg/dL, and 2-h PPG added predictive power to FPG measures.[17] An epidemiological investigation collected from 14 long-term observational studies suggested that elevated PPG values contributed to an approximate three-fold increase in the risk of developing coronary heart disease or cardiovascular events.[18] Moreover, in T2D, PPG was a strong predictor of cardiovascular events and all-cause mortality during long-term follow-up.[19]

Although less skill and equipment are required to measure FPG and PPG as indicators of glycemic concentration, some limitations are still present. FPG results are affected by short-term lifestyle changes such as stress, overactivity, medications and acute perturbations in glucose levels.[20] FPG alone is less sensitive for the assessment of glycemic control, but is used to detect groups at high risk for the development of diabetes and is more practical and less expensive than the oral glucose tolerance test (OGTT).[21] PPG results can be affected by carbohydrate intake, duration of fasting prior to the test, the timing of the test, and activity or carbohydrate intake during the test.[22] These 2 measures can also be affected by factors such as the blood collection, storage, skill of the technician, and sensitivity of the method used for detection.[21,22] Therefore, these 2 biomarkers cannot be used to assess glycemic control clinically or biochemically because of their inaccurate results.[23]

Glycated hemoglobin

HbA1c is formed from the posttranslational modification of Hb A by the nonenzymatic covalent binding of glucose to the N-terminal valine of the β-globin chain.[10] The percentage of HbA1c in the total Hb reflects glycemic control during the lifecycle (2 to 3 months) of a red blood cell (RBC).[24] Using HbA1c rather than BG for diabetic screening, diagnosis, and management is advantageous because of its relative insensitivity to preanalytical variables such as acute stress and its lower within-patient biological variability and broad diurnal variation.[25] Therefore, HbA1c has been considered the gold standard biomarker for the last 2 decades, and it is a universally accepted means for monitoring glycemic control and a clinical surrogate endpoint in diabetes.

HbA1c is linked with the development of long-term diabetic complications. A 1% increase in absolute concentrations of HbA1c was associated with an increase of approximately 10% to 20% in cardiovascular disease (CVD) risk.[26] In a large prospective cohort study, increased HbA1c levels were an independent risk factor for CVD in patients with T2D.[27] Similar results were observed in a retrospective study, suggesting that increased HbA1c level is an independent predictor of complex coronary lesions among older patients with diabetes.[28] However, some large trials

Table 1. Characteristics of traditional and nontraditional biomarkers for glycemic control.

Biomarker	Mechanism of action	Time span of glycemic control	Advantages	Limitations	Association with dysglycemia
FPG	Measures fasting BG levels[20]	8 to 10 h	Less skill and equipment required FPG levels exceeding 126 mg/dL are associated with an increased risk of mortality[17] Current glycemic status is determined with a relatively simple, accurate, and inexpensive test for daily diabetes management SMBG[20] Detection of high-risk groups for diabetes development[21]	Affected by short-term lifestyle changes such as overactivity, stress, drugs, and acute perturbations in glucose levels[20] Less sensitive for assessing glycemic control[21]	Elevated FPG is associated with prediabetes and diabetes[20]
PPG	Measures postprandial BG levels[20]	2 to 4 h	Less skill and equipment required Stronger predictor of cardiovascular events and all-cause mortality[18,19] Acute assessment of glycemia and provision of vital information with regard to risk that HbA1c or FPG cannot provide[20]	Affected by carbohydrate intake, duration of fasting preceding the test, the timing of the test, and activity or carbohydrate intake during the test[22]	Elevated 2-h PPG is associated with prediabetes and diabetes[20]
HbA1c	Formed from the osttranslational modification of hemoglobin A by the nonenzymatic covalent binding of glucose to the N-terminal valine of the β-globin chain[10]	2 to 3 mo	More reliable biomarker of chronic glycemia[24] Less sensitive to several preanalytical variables, lower within-patient biological variability, no broad diurnal variations, no patient preparation required, not influenced by acute stress[25] Associated with diabetes complications[26-28] Standardized[35]	Affected by the lifespan of erythrocytes and BG levels[10,15,30,44] Affected by hemoglobin variants and the analytical methods used to measure HbA1c[31] Physiological interference[39,40] Biological confounders[41-43]	Elevated HbA1c reflects chronic glycemia[10]
FA	Produced by the spontaneous nonenzymatic glycation of glucose with the amino groups of total serum proteins[49]	2 to 3 wk	Simple, specific, easily automated, widely available, inexpensive, and fasting not required[44] Identifies fluctuating glucose levels under stable HbA1c[44] Strong correlation with HbA1c[50] Strongly associated with diabetic nephropathy[52] Useful for identifying high risk of abnormal glucose tolerance among pregnant women[54] Associated with the prediction of incident diabetes[70,71]	Affected by the profiles and concentrations of the serum proteins[56] Unreliable in conditions with altered serum albumin[57] Affected by rapid albumin turnover (liver disease, nephrotic syndrome, protein-losing enteropathies)[58] Unreliable under conditions with raised total protein (multiple myeloma, polyclonal gammopathies)[58]	Increased FA indicates high glucose levels[50]

GA	Proportion of albumin that is glycated[59]	2 to 3 wk	Not influenced by the lifespan of erythrocytes, anemia, hemoglobinopathies, or other conditions such as autologous blood donations, liver cirrhosis, and human immunodeficiency virus[62,63] More accurately reflects glycemic control compared with HbA1c and FA in the case of severe CKD (stage 4 and 5)[64] More accurate assessment for predicting the development of diabetes complications and comorbidities compared with HbA1c[63] More accurate assessment of recent glycemic control for treatment modifications in gestational and neonatal diabetes[68,69] Associated with the prediction of incident diabetes[70,71]	Unreliable in conditions with serum protein and albumin metabolism changes[44,74] Falsely indicates low levels in the case of obesity[72,73] Falsely indicates low levels in infants compared with in adults, and correlated with both age and serum albumin[75] Influenced by genetic variants that correlate with both glycemic and nonglycemic factors[76]	Associated with the prediction of incident diabetes[70,71]
1,5-AG	1,5-AG is a metabolic dietary polyol that is structurally similar to glucose and competes with extremely high levels of glucose for renal tubular reabsorption[77]	1 to 2 wk	Possible prediction of incident diabetes[71] Associated with gestational diabetes and macrosomia[77] Fasting not necessary, more accurate postprandial glycemic excursions, and more sensitive and specific than HbA1c and FA[79] Reliable marker of glycemic control in T2D with CKD stage 1 to 3[80] Associated with diabetes complications[77,81-83]	Affected by diet, sex, and race[15] Limited in patients with renal tubular acidosis, stage 4 to 5 CKD, ESRD, and renal glycosuria, and in those treated with SGLT-2i or acarbose[77,80] Relatively expensive, limited standardization, and cannot identify hypoglycemia[84] Affected by changes in the renal threshold for glucose[84]	Lower 1,5-AG levels are associated with prediabetes and diabetes[71]
CGM	Measures the glucose levels in the body's interstitial fluid at 1-to-5-min intervals, providing near real-time glucose data[85]	10 to 14 d	Measures valuable glycemic information such as mean glucose exposure and GV as well as trends in hypoglycemia and hyperglycemia that are often missed with SMBG[87] Monitors time spent in the target BG range and reduces incidence of severe hypoglycemic events[90] Improvement of diabetic outcomes in various vulnerable populations of patients with diabetes[93-101] Dramatically increased time spent in normoglycemia with a concomitant marked reduction in the frequency of hypoglycemia compared with SMBG[101]	Expensive, limited availability, and insurance-related limitations and reimbursement problems[87] Hindered by community-related attitudes among patients and health care providers[87] Periodic replacement of sensors[87] Lack of approval for use of CGM data for the adjustment of insulin-dosing in ambulatory, hospital, and intensive care settings[87] Relatively inaccurate in the lower glucose range; recommended to be used in conjunction with SMBG[102]	Measures interstitial glucose levels semicontinuously, and translates them into dynamic data to indicate glucose flow direction and rate of change[85]

FPG: fasting plasma glucose; PPG: postprandial plasma glucose; HbA1c: glycated hemoglobin; OGTT: oral glucose tolerance test; FA: fructosamine; GA: glycated albumin; CKD: chronic kidney disease; 1,5-AG: 1,5-anhydroglucitol; T1D: type 1 diabetes; T2D: type 2 diabetes; ESRD: end-stage renal disease; SGLT-2i: sodium glucose cotransporter 2 inhibitors; CGM: continuous glucose monitoring; SMBG: self-monitoring of blood glucose; GV: glycemic variability.

such as ADVANCE and the Action to Control Cardiovascular Risk in Diabetes failed to significantly reduce major cardiovascular events after lowering HbA1c levels in patients with long-term diabetes.[7,8] This differs from the effects of intensive glycemic control on the reduction of microvascular complications.

Scholars have examined HbA1c in relation to average glycemic control by using a wide range of BG results. HbA1c levels are influenced by the lifespan of erythrocytes and BG levels and therefore reflect hyperglycemic exposure to erythrocytes over the preceding 8 to 12 weeks prior to measurement.[29] Approximately 50% of HbA1c values reflect glucose levels over the previous 30 days, and 40% and 10% are reflective of the exposure during the previous 31 to 90 and 91 to 120 days, respectively.[30] Thus, only 25% of all HbA1c values reflect the glycemic index for the previous 60 to 120 days.[30]

HbA1c synthesis and management could be disrupted by Hb variants, depending on the nature of the congenital disorder, which may affect the synthesis and analysis used to measure HbA1c.[31] Structural Hb variants result from the point mutations of protein chains; approximately 99% belong to the 4 categories S, C, E, and D.[31] The most common Hb-related interferences from a synthetic variant are thalassemia traits, HbC, HbE, HbF, and HbS.[32] Derivative variants of Hb such as carbamylation derived from uremic toxins in chronic kidney disease (CKD), especially end-stage renal disease (ESRD), may cause changes in erythrocyte lifespan that interfere with the results and interpretation of HbA1c assays.[33] The analytical interference of an Hb variant is assay- and variant-specific; thus, generalizing the effects of Hb variants based upon assay type and substitution has proved difficult.[34] Notably, the majority of interferences have been mitigated through improvements in analytical methodologies, and the remaining interferences have been identified and rigorously scrutinized. A comprehensive list of the susceptibility of different HbA1c assays to various interferences and Hb variants is regularly updated on the National Glycohemoglobin Standardization Program website.[35]

The potential effects of RBC transfusion on HbA1c has been long recognized, but opinions on the specific effects are divergent.[36-38] RBC transfusion leads to an underestimation or overestimation of the actual values of HbA1c in patients with diabetes because the introduced hemoglobin molecules exposed to glucose concentrations may differ from the glucose concentrations in the recipient who received transfusion. Several studies have demonstrated that the high glucose concentration in RBC storage medium promotes glycation and further increases HbA1c values over time, indicating that HbA1c values may increase in transfused patients.[36,37] However, in other studies, RBC transfusion reportedly reduced the HbA1c concentration in patients with diabetes.[38] Decreased HbA1c posttransfusion was most pronounced in patients who received large transfusion volumes and/or had a high pretransfusion HbA1c level as a result of the dilutional effect caused by RBCs containing typical amounts of HbA1c. Moreover, patients with the highest pretransfusion HbA1c values exhibited the largest decreases after transfusion.[38] Further large-scale studies are required to clarify the effect of RBC storage conditions on HbA1c and the overall effect of RBC transfusion on HbA1c in patients with diabetes.

Physiological factors associated with HbA1c such as race, genetic predisposition, and age are major determinants influencing the accuracy of its measurement and have emerged as a considerable challenge. HbA1c concentrations have been reported to be higher among Black, Hispanic, American Indian, and Asian populations compared with Caucasian populations independent of the differences in age, sex, education, marital status, blood pressure, body mass index, hematocrit measurements, pre- and

postprandial glycemia, beta-cell viability, and insulin resistance.[39] Similarly, in a meta-analysis, significant differences were recorded in the HbA1c concentrations of Black (0.26%; $p < 0.001$), Asian (0.24%; $p < 0.001$), and Latino (0.08%; $p < 0.001$) groups compared with those of the Caucasian population.[40] Therefore, these differences may affect the use of HbA1c as the sole indicator of diabetes diagnoses in all populations.

A significant positive association between HbA1c concentration and age was observed in nondiabetic populations independent of sex and glycemic level, suggesting that the clinical accuracy of this assay can be improved by age-specific reference intervals and clinical cut-off points in both diabetic diagnosis and treatment.[41] In many genetic studies, researchers suggested that multiple genetic loci influence HbA1c through glycemic pathways, which may provide a possible explanation for the physiological variability and improve the clinical utility of this valuable biomarker through a more individualized approach.[42] Meta-Analysis of Glucose and Insulin-related Traits Consortium investigators successfully identified 60 genetic variants influencing HbA1c, of which 19 were associated with glycemic pathways, 22 were associated with erythrocytic pathways, and 19 remained unclassified.[43] Glucose-6-phosphate dehydrogenase (G6PD) deficiency has implications for the diagnostic accuracy of HbA1c. A variant on the X chromosome coding for G6PD was associated with significantly higher HbA1c variability in populations with African ancestry compared with that in other racial groups.[43] This highly prevalent variant is linked with shortened erythrocyte lifespan and has crucial implications for the management of diabetes, with carriers of the HbA1c-lowering G6PD allele requiring adjusted HbA1c treatment targets.[43]

The key nonglycemic factors affecting HbA1c levels are the concentration and viability of erythrocytes. The half-life of HbA1c is directly associated with erythrocyte lifespan, which ranges from 3 to 4 months.[10] Therefore, any factor affecting the lifespan and production of erythrocytes can affect the HbA1c level, thereby decreasing its specificity and sensitivity for the diagnosis and control of diabetes.[15] Hence, low HbA1c concentrations may result from any condition that shortens erythrocyte lifespan or is associated with increased RBC turnover, which shortens the exposure of the cell to glucose (e.g., ESRD, hemolysis, erythropoietin therapy, acute and chronic blood loss, splenomegaly, pregnancy, iron therapy, and use of supplements and medications such as ribavirin and interferon-alpha).[44,45] By contrast, high HbA1c concentrations may result from any condition that prolongs erythrocyte lifespan or is associated with decreased RBC turnover, which exposes the cell to glucose for a long period of time (e.g., asplenia, severe hypertriglyceridemia, severe hyperbilirubinemia, chronic alcohol consumption, uremia, post splenectomy, iron deficiency anemia, and folate or vitamin B12 deficiency anemia).[44,45] Additionally, for patients who have ingested vitamin C, correct measurement of HbA1c is exceedingly difficult; this vitamin can increase or decrease HbA1c when measured using electrophoresis or chromatography, respectively, because of the competitive inhibition of glycosylation.[45] Similarly, in patients with hemoglobinopathies (e.g., thalassemia and sickle cell anemia), HbA1c levels may be falsely increased or decreased as a result of the presence of other glycated products derived from variant forms of adult hemoglobin (HbA) in addition to HbA1c.[46] Finally, during neonatal periods, fetal HbA is the main hemoglobin, with HbA accounting for less than 10% of the total hemoglobin. Therefore, HbA1c does not accurately reflect glycemic control and must not be used as a biomarker for neonatal diabetes.[47]

The optimal control of glycemic variability (GV) is a key strategy in the reduction and prevention of CVD in diabetes . The most

notable disadvantage of HbA1c is its inability to capture short-term glycemic changes and predict hyperglycemia. Moreover, HbA1c correlates mainly with sustained chronic hyperglycemia but not with GV in patients with well-controlled T2D.[48] However, this must be taken into account for patient safety and the timely adjustment of antihyperglycemic agents as well as clinical decision-making. Thus, alternative biomarkers have been considered for short-term glycemic control. A comprehensive list of physiological, biological, and pharmacological factors that may influence the synthesis, measurement, and interpretation of HbA1c is presented in Table 2.

Fructosamine

Fructosamine (FA) is a ketoamine produced by the spontaneous nonenzymatic glycation of glucose with amino groups of plasma proteins.[49] FA values reflect short-term glycemic control through retrospective assessment of the mean BG concentrations over the previous 2 to 3 weeks, potentially lessening the confounding effect of shortened or increased erythrocyte turnover observed in HbA1c levels.[49] Hence, FA can be used clinically as a substitute for HbA1c to reflect changes in glycemic control. The assay is simple, specific, and can be automated, thus enabling samples to be collected quicker and more cost-effectively than with HbA1c assays.[44] However, unlike HbA1c assays, little standardization is in place across different FA assays.

FA may be useful for identifying fluctuate in glucose levels in patients with diabetes who exhibit stable HbA1c.[44] Several studies have demonstrated a strong correlation between serum FA and HbA1c.[50] Research into patients with diabetes and stage 3 or 4 CKD recorded a strong correlation between FA levels and well-controlled glycemia; however, the estimated mean glucose level was substantially underestimated.[49,51] Increased serum FA levels in patients with diabetes are strongly associated with the progression of diabetic nephropathy (DN).[52] FA levels are also significantly clinically associated with DN-related risk factors such as markers of glycemic control (e.g., HbA1c), renal insufficiency, obesity, and hypertension in the development of micro- and macrovascular complications.[52]

Values of serum FA paired with fasting blood glucose or random BG could assist in filtering high-risk individuals based on OGTTs, thus avoiding glucose challenges in pregnant women.[53] Conversely, serum FA was reported to be useful for identifying pregnant women at high risk of abnormal glucose tolerance, but it could not be employed to predict gestational diabetes during early pregnancy because of the lack of correlation with OGTT results.[54] Moreover, serum FA levels in pregnant women are influenced by both maternal and gestational age; thus, the use of FA is complicated for screening and diagnosing diabetes in pregnant women.[55] Further studies are required to establish specific reference ranges throughout the course of pregnancy to increase the diagnostic efficiency of FA.

Other limitations affect the indication capacity of this biomarker for glycemic control. FA is influenced by the profile and concentrations of serum proteins because only a fraction (approximately 10%) of the total glycated serum proteins represent FA.[56] Therefore, serum FA levels must be adjusted if the serum albumin value is abnormal.[57] FA assay is also unreliable if the serum albumin is less than 3.0 g/dL, and false low levels of serum FA can occur as a result of rapid albumin turnover, such as with liver disease, nephrotic syndrome, and protein-losing enteropathies.[58] By contrast, serum FA may present with false high levels under conditions of raised total protein, such as in multiple myeloma and polyclonal gammopathies.[58]

Glycated albumin

Glycated albumin (GA) is also a ke-

Table 2. Physiological, biological, and pharmacological factors influencing the synthesis, measurement, and interpretation of HbA1c.

Condition	Effect on HbA1c	Proposed mechanism(s)	Ref.	Remarks
ESRD	False decrease	Likely as a result of chronic anemia combined with decreased RBC survival rate	44,45	[*] HbA1c levels decrease during the second trimester and rise during the third trimester
Hemolysis	False decrease	Decreased RBC survival rate		
Erythropoietin therapy	False decrease	New RBCs are added to the existing pool resulting in a low glycation rate because of the reduced circulation time. The proportion of novel RBCs to old ones reportedly exhibits a sharp increase		
Acute and chronic blood loss	False decrease	Decreased RBC survival rate		
Splenomegaly	False decrease	Decreased RBC survival rate		
Pregnancy[*]	False decrease	Decreased RBC survival rate		[†] When triglyceride concentrations are greater than 1,750 mg/dL
Iron therapy	False decrease	Likely as a result of increased bone marrow erythropoiesis on treatment, leading to the production of immature erythrocytes		
Vitamin E	False decrease	Reduced protein glycation		
Ribavirin, interferon-alpha	False decrease	Likely results in hemolytic anemia, leading to a decreased RBC survival rate		[‡] When bilirubin concentrations are greater than 20 mg/dL
Asplenia	False increase	Increased RBC lifespan		
Severe hypertriglyceridemia[†]	False increase	Mechanism remains unclear. Lipemic blood samples may have higher values than the actual measurement of HbA1c		
Severe hyperbilirubinemia[‡]	False increase	Mechanism remains unclear		
Chronic alcohol consumption	False increase	Formation and detection of hemoglobin A1-acetaldehyde		[l] Generally, HbA1c is unreliable for homozygous hemoglobinopathies but is reliable for heterozygous hemoglobinopathies
Uremia	False increase	Excessive amount of cyanate derived from urea, which causes carbamylation at the N-terminal valine residue. This carbamylated hemoglobin results in the increased levels of HbA1c		
Iron deficiency anemia	False increase	Mechanism remains unclear. The quaternary structure of the hemoglobin molecule during iron deficiency may be altered; glycation of the β-globin chain occurs more readily in the relative absence of iron. Under conditions of prolonged iron deficiency, the RBC production rate decreases, leading to anemia, an increased average age of circulating RBCs and, in turn, increased HbA1c		
Folate or vitamin B12 deficiency	False increase	Increased protein glycation		[#] Studies using contemporary HbA1c methods to investigate the effect of RBC storage conditions on HbA1c and the overall effect of RBC transfusion on HbA1c are limited
Splenectomy	False increase	Increased RBC lifespan		
Infection or tumor-related anemia	False increase	Decreased erythropoietin production, leading to increased RBC lifespan		
Lead poisoning	False increase	Mechanism remains unclear		
Vitamin C ingestion	False increase/ decrease	Measurement with electrophoresis may indicate increased HbA1c levels. Measurement with chromatography may indicate decreased HbA1c levels as a result of the inhibition of glycosylation through a competitive mechanism		
Hemoglobinopathies[l]	False increase/ decrease	Dependent on the nature of the congenital disorder affecting hemoglobin synthesis and the analytical method used		
RBC transfusion[#]	False increase/ decrease	High glucose concentration in RBC storage medium promotes glycation and causes HbA1c levels to increase. Decreased HbA1c levels are exhibited in patients who receive large transfusion volumes and/or have a high pretransfusion HbA1c as a result of the dilutional effect of RBCs containing typical amounts of HbA1c		

HbA1c: glycated hemoglobin; ESRD: end-stage renal disease; HbA: hemoglobin A; RBC: red blood cell.

toamine formed through nonenzymatic glycation. In contrast to FA assays, which measure total glycated serum protein (mostly albumin, but also immunoglobulins and other circulation proteins), GA assays measure the proportion of the total albumin that is glycated. Because the turnover of serum GA is more rapid than that of erythrocyte, GA is a more useful biomarker for reflecting short-term glycemic control (2 to 3 weeks) in diabetes than is HbA1c.[59] Unlike FA, GA levels do not correlate with serum albumin levels and are approximately 3 times higher than those of HbA1c. Additionally, albumin exhibits 10 times faster glycation by glucose than does HbA1c, indicating that GA may more accurately reflect GV and glucose excursions.[60,61]

GA provides several advantages over other biomarkers for monitoring and assessing glycemic control. Its values are unaffected by erythrocyte lifespan, anemia, hemoglobinopathies, or circumstances such as autologous blood donations, liver cirrhosis, and human immunodeficiency virus, which may all induce artificially low HbA1c levels.[62,63] In the case of stage 4 and 5 CKD, GA more accurately reflects glycemic control in comparison to HbA1c and FA and is thus the preferred indicator.[64] Two cross-sectional studies from the United States and Japan involving patients with diabetes undergoing hemodialysis have recognized GA as better biomarker of glycemic control than HbA1c.[65,66] Furthermore, researchers have identified significantly lower GA/HbA1c ratios in patients with diabetes without DN compared with those on dialysis, suggesting an underestimation of glycemic control by HbA1c under these conditions. This phenomenon is potentially attributable to reduced erythrocyte survival and transfusions lowering the HbA1c levels in patients with diabetes on hemodialysis.[67]

Compared with HbA1c, GA provided more accurate assessment of the development of diabetes complications and comorbidities in several cross-sectional studies.[63] GA can detect changes in glycemia earlier than can HbA1c and is thus a more suitable biomarker for short-term glycemic control, particularly for treatment modifications in gestational and neonatal diabetes.[68,69] In several studies, both GA and FA were associated with the prediction of incident diabetes,[70,71] with GA levels exhibiting a 15% to 16% association with diabetes in Asian populations.[72,73]

However, GA measurement is unreliable in clinical situations that can affect albumin and protein metabolism. An increase in albumin metabolism results in low GA concentrations, such as in cases of hyperthyroidism, Cushing's syndrome, nephrotic syndrome, and glucocorticoid therapy and in neonates.[44] By contract, a decrease in albumin metabolism results in high GA concentrations in conditions such as hypothyroidism and liver cirrhosis.[44] Moreover, body mass index is negatively correlated with GA but not with HbA1c in patients with diabetes.[74] Decreased GA levels in those diagnosed as having obesity are possible as a result of increased albumin catabolism and decreased rate of albumin synthesis from obesity-associated inflammation. Nevertheless, the precise mechanism underlying low GA in obesity remains unclear.[72,73] GA levels were lower in infants than in adults and were correlated with both age and serum albumin.[75] This phenomenon is attributed to the lower serum glucose levels in infants compared with those in adults, and the high albumin metabolism associated with low GA levels. Finally, similar to HbA1c, GA is influenced by genetic variants that are correlated with both glycemic and nonglycemic factors, both of which must be considered during clinical interpretation of the results.[76]

1,5-anhydroglucitol

1,5-anhydroglucitol (1,5-AG), a 1-deoxy form of glucose, is a short-term indicator for glycemia, reflecting hyperglycemic glucose within a retrospective period of 1 to 2 weeks.[77]

Largely derived from food such as soybeans and absorbed by the intestine at a static rate, this metabolic dietary polyol is structurally similar to glucose and competes with extremely high glucose levels for renal tubular reabsorption. Therefore, in conditions such as CKD and pregnancy, the 1,5-AG level must be carefully interpreted because any renal function changes may influence the threshold for glucose excretion. Serum 1,5-AG levels are drastically reduced when glucose concentrations exceed the renal threshold for glycosuria.[78] Hence, low 1,5-AG levels indicate both high BG levels and hyperglycemic excursions.[79]

1,5-AG levels remain unaffected by mild or moderate renal dysfunction, signifying that its reliability as a biomarker of glycemic control in patients with T2D and CKD stages 1 to 3.[80] Its use is limited in patients with renal tubular acidosis, CKD stages 4 to 5, ESRD, and renal glycosuria as well as in those treated with sodium glucose cotransporter 2 inhibitors and acarbose.[77,80] 1,5-AG measurements can reflect postprandial glycemic excursions and are more sensitive and specific than HbA1c and FA measurements. Thus, 1,5-AG may be useful in combination with HbA1c to estimate glycemic control in patients with moderately controlled diabetes.[79] 1,5-AG was also suggested to predict incident diabetes, but observed associations were lower in magnitude compared with those of other hyperglycemic biomarkers and were not present in individuals with fasting glucose or HbA1c within the nondiabetic range.[71] The low serum 1,5-AG level is a predictor of micro- and macrovascular complications in patients with diabetes[77,81] and may also be an indicator for acute ischemic stroke and transient ischemic attack in patients with well-controlled diabetes.[82] In a prospective study of 2,095 people (including approximately 100 patients with diabetes), 1,5-AG was associated with incident CVD during the 11-year follow-up.[83] Furthermore, decreased 1,5-AG levels were linked to an increased risk of gestational diabetes and macrosomia.[77]

However, the relative expense and lack of standardization limit the application of 1,5-AG. Although 1,5-AG is a useful biomarker for daily glycemic excursions in patients with well-controlled T2D, it cannot identify hypoglycemia[84] nor assess GV. Moreover, glucose levels of more than 180 mg/dL result in rapid reduction of 1,5-AG,[84] and the diet, sex, and race of an individual affect this measurement.[15] Further studies are warranted to examine 1,5-AG as a n indicator of glycemic control, particularly in patients with T1D, varying levels of alternative biomarkers, and different magnitudes of glucose variability as well as in situations where the clinical value of alternative biomarkers is limited.

Continuous glucose monitoring systems

SMBG allows patients with diabetes to conveniently monitor their BG concentrations at any time and adjust or verify the effect of their treatment based on the result. Although broadly applied for glycemic control, SMBG typically reflects single glucose values at a particular timepoint, providing only a snapshot of the entire glucose picture, with no capability to detect the rapid changes occurring between single measurements.[67] By contrast, continuous glucose monitoring (CGM) tracks glucose concentrations in the body's interstitial fluid at 1-to-5-min intervals, offering almost real-time glucose data. CGM data over a period of 10 to 14 days provides a sufficient estimate of glucose metrics for a 3-month period.[85] Thus, HbA1c can be estimated (eA1c) from this mean glucose value using a standard formula if 70% to 80% of CGM readings are available.[86]

CGM provides valuable information previously unattainable for glycemia such as mean glucose exposure, GV, and hypo- and hyperglycemic trends, which are often missed with SMBG. CGM is recommended for patients with frequent, severe, or nocturnal hypoglyce-

mia, especially in the presence of hypoglycemia unawareness.[87] Clinically, GV is major risk factor because exaggerated glucose fluctuations are linked to the increased development of micro- and macrovascular complications primarily attributable to hypoglycemia, which are not reflected by HbA1c.[13,88] Monitoring time spent in the target BG range, referred to as the time in range (TIR) (glucose 70 – 180 mg/dL), is becoming the new standard for patients and health care providers.[89] The use of CGM offers increased TIR and reduced incidence of severe hypoglycemic events.[90]

Alternative modalities for determining CGM trends include real-time continuous glucose monitoring (rtCGM), which provides real-time data on glucose trends, direction, and rate of change, and intermittently scanned glucose monitoring (iCGM), which provides continuous glucose measurements retrospectively.[86] Various metrics have been proposed to assist physicians in accurate clinical assessment of glycemic status in patients with diabetes.[91] In accordance with to the expert opinion of an international consensus group, 3 core CGM metrics were designated for use in clinical practice, namely the percentage of readings and per day TIR, time below range (TBR; glucose $\leq$ 69 mg/dL), and time above range (TAR) (glucose $\geq$ 181 mg/dL); an increased TIR and reduced TBR is considered the primary glycemic goal to achieve effective and safe glycemic control.[91] A meta-analysis of 15 randomized controlled trials (RCTs) included a comparison of CGM and conventional therapy, which demonstrated that CGM improved glycemic control by increasing the TIR and reducing the TBR, TAR, and GV in both T1D and T2D.[92] Moreover, rtCGM facilitated improvement in HbA1c, the TIR, and the TAR, whereas iCGM was associated with a marked decline in the TBR.[92]

The advantage of applying CGM to improve diabetic outcomes has been demonstrated in numerous studies on various vulnerable populations of patients with diabetes such as pregnant woman,[93-95] adolescents and young adults,[96] children with hypoglycemic episodes,[97] the hospitalized patients,[98] the elderly,[99] the patients with suffering from diabetic kidney disease[100] and from impaired awareness of hypoglycemia.[101] These studies confirm that CGM is a technology that can be effectively used by patients with diabetes to improve glycemic control. Therefore, broadening the use of CGM is feasible in primary care for improvement of diabetic control and reduction of diabetic complications, particularly among the populations most in needed.

Despite these advantages, many clinical barriers impede the implementation of this technology for the management of diabetes.[87] Current CGM systems are expensive and not easily available in clinical practice; moreover, in most countries, insurance-related agencies do not cover or reimburse for CGM. Patient and healthcare provider's community-related attitudes may hinder the broad application of this technology. The periodic and necessary replacement of sensors contributes to the cost, inconvenience, and slow user acceptance. The lack of approval for the use of CGM data for the adjustment of insulin-dosing in ambulatory, hospital, and intensive care unit settings also impedes widespread adoption and negatively affects reimbursement. Additionally, CGM systems are relatively inaccurate in the lower glucose range and must be used in conjunction with SMBG.[102] Nevertheless, recent advancements in technology and dedicated research have addressed several of these problems. The International Consensus on Use of Continuous Glucose Monitoring represented great progress in its provision of technical and clinical recommendations on the use of CGM, which complement HbA1c for a wide range of patients with diabetes. This work offered insight and comprehensive evidence across the advanced metrics of CGM-derived data to improve glycemic control and clinical outcomes.[86]

Conclusions

Diabetes is a chronic metabolic disease characterized by chronic hyperglycemia, which must be strictly controlled and maintained within an optimal range to reduce the risk of diabetic complications. Despite analytical interferences and biological confounders, HbA1c remains the key biomarker for long-term glycemic control. Nevertheless, increasing attention has been paid to nontraditional biomarkers that provide valuable information for the management of diabetes as complementary measures, particularly in cases where a HbA1c assay is insufficient or unreliable to estimate the potential risk of adverse outcomes. FA can be used to identify fluctuating glucose levels in patients with diabetes with stable HbA1c, and a strong correlation has been noted between HbA1c and serum FA. GA can detect changes in glycemia earlier than HbA1c and is thus a more accurate indicator of recent, short-term glycemic control, which is particularly useful early treatment modification. In addition, 1,5-AG is a useful indicator for assessing within-day glucose excursions. The complementary character of these different assays of hyperglycemia offers the possibility to explore the application of FA, GA, and 1,5-AG in the development of risk prediction models for diabetes and its resultant complications. CGM provides valuable information previously unattainable for glycemia such as mean glucose exposure, GV, and hypo- and hyperglycemic trends, which are often missed with SMBG. One or more of these nontraditional biomarkers may be an efficient and appropriate substitute for HbA1c in some patients, and strategies that combine multiple assays for glycemia may be beneficial in certain cases. Cross-sectional and prospective studies on the complementary nature of these nontraditional tests of hyperglycemia (beyond HbA1c and glucose) have made valuable contributions, but much remains to be characterized. Additional studies on the sole or complementary use of these alternative glycemic biomarkers are required for the early diagnosis, management, and prevention of long-term complications in diverse populations of patients with diabetes.

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