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Evaluation of Glycated Albumin (GA) and GA/Hba1c Ratio for Diagnosis of Diabetes and Glycemic Control: A Comprehensive Review

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Abstract

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by chronic high blood glucose concentrations (hyperglycemia). When it is left untreated or improperly managed, it can lead to acute complications including diabetic ketoacidosis and non-ketotic hyperosmolar coma. In addition, possible long-term complications include impotence, nerve damage, stroke, chronic kidney failure, cardiovascular disease, foot ulcers, and retinopathy. Historically, universal methods to measure glycemic control for the diagnosis of diabetes included fasting plasma glucose level (FPG), 2-h plasma glucose (2HP), and random plasma glucose. However, these measurements did not provide information about glycemic control over a long period of time. To address this problem, there has been a switch in the past decade to diagnosing diabetes and its severity through measurement of blood glycated proteins such as Hemoglobin A1c (HbA1c) and glycated albumin (GA). Diagnosis and evaluation of diabetes using glycated proteins has many advantages including high accuracy of glycemic control over a period of time. Currently, common laboratory methods used to measure glycated proteins are high-performance liquid chromatography (HPLC), immunoassay, and electrophoresis. HbA1c is one of the most important diagnostic factors for diabetes. However, some reports indicate that HbA1c is not a suitable marker to determine glycemic control in all diabetic patients. GA, which is not influenced by changes in the lifespan of erythrocytes, is thought to be a good alternative indicator of glycemic control in diabetic patients. Here, we review the literature that has investigated the suitability of HbA1c, GA and GA:HbA1c as indicators of long-term glycemic control and demonstrate the importance of selecting the appropriate glycated protein based on the patient's health status in order to provide useful and modern point-of-care monitoring and treatment.

Keywords: Glycated hemoglobin; glycemic control; diabetes; diagnosis; GA:HbA1c; glycated albumin

1. Introduction

Currently, with three million diabetics in the USA and over three million worldwide, it is expected that the number of diabetic patients will reach 552 million by 2030 [[1]]. Diabetes is a group of disorders characterized by chronic elevations in blood glucose (hyperglycemia) and resulting from insulin deficiency and/or insulin resistance [[3]]. Insulin is a hormone that is made by pancreatic β-cells and signals tissues around the body to uptake glucose, which is essential for many metabolic processes [[5]]. Insulin deficiency or insulin resistance in diabetes causes hyperglycemia as the body's tissues are not able to remove sufficient glucose from the bloodstream [[13]]. Hyperglycemia increases the risk of kidney disease, heart disease and stroke, lower limb amputations and blindness [[14]].

There are two prevalent types of diabetes: (a) Type 1 diabetes (T1D), typically called insulin-dependent, is an autoimmune disease in which the body's immune system attacks the insulin-producing pancreatic β-cells and ~5–10% of diabetics have T1D [[1]] and (b) Type 2 diabetes (T2D), historically called adult-onset and currently called non-insulin dependent diabetes, is the most common type of diabetes and 90–95% of diabetics have T2D [[1]]. T2D is significantly positively associated with parameters, such as age, family history and obesity [[2]]. It

occurs as a result of an insufficient cellular response to insulin [[1]]. The detection of diabetes is dependent on the detection of hyperglycemia in the blood (fasting glucose ≥126 mg/dL [7.0 mmol/L]; random plasma glucose of ≥200 mg/dL [11.1 mmol/L]) [[19]] and signs and symptoms of hyperglycemia.

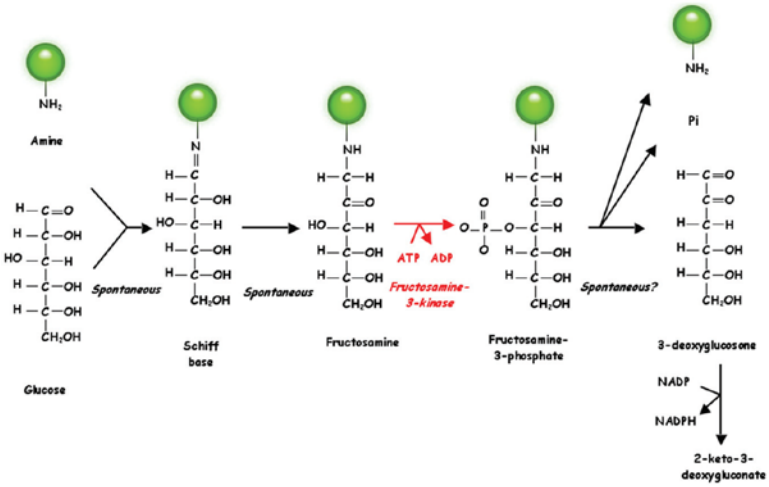
Many of the adverse physiological effects of diabetes are associated with the process of protein glycation [[13]]. Protein glycation includes the addition of reducing sugars and/or their reactive degradation products to primary or secondary amine groups on proteins (summarized in section 2) [[13], [20]]. Glycated proteins also provide a measure of glycemic control over a period of time. Given the importance of glycated proteins to diabetes management and progression it is important to assess glycated proteins in diabetics for medical and scientific applications [[21]]. In accordance with this, there has been a switch in the past decade to diagnosing diabetes presence and severity through measurement of blood glycated proteins such as glycated albumin (GA) and hemoglobin A1c (HbA1c) [[22]]. In this review, we discuss the literature that has investigated the suitability of GA and HbA1c and GA/HbA1c ratio at determining glycemic control for diabetics with different health conditions.

2. Indicators of glycemic control

Fructosamine, GA and HbA1c, are glycated proteins that are used to evaluate glycemic control in diabetic patients [[23]]. The N-terminus of a protein can act as a potential site for the formation of an early stage Amadori product which can go on to become an advanced glycation end product (AGE). AGEs can be formed through glycation by fructosamines, GA and HbA1C [[13]].

2.1. Fructosamine

Fructosamine is a general term applied to identify all glycated proteins, including GA. Since, the lifetime of fructosamine is shorter than HbA1c, it is a more helpful tool for assessing glycemic control. Fructosamine-3-kinase (FN3K) is a biomarker of fructosamines (Figure 1). Recently, the concept of enzymatic deglycation has been significantly enhanced by the molecular characterization of the deglycating enzyme FN3K and demonstration that FN3K-mediated deglycation of hemoglobin actually occurs *in vivo*. This reversal of non-enzymatic glycation occurs because the phosphorylation of fructoselysin on proteins by FN3K to fructoselysin-3-phosphate (FL3P) creates a compound which is mostly unstable and spontaneously decomposes to lysine, 3-deoxyglucosone and inorganic phosphate [[25]].



Graph: Figure 1. Mechanism of fructosamine-3-kinase formation [[27]].

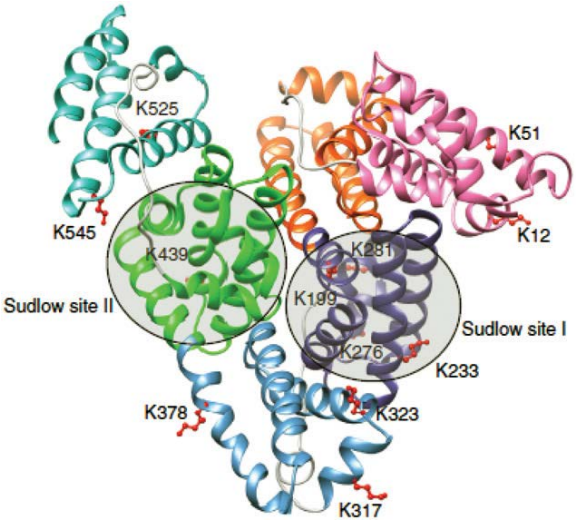
Although, it is known that fructosamine concentration is typically corrected for total protein, this practice still remains controversial [[25]]. Fructosamine is not affected by changes in hemoglobin metabolism, but can be

influenced by disorders in protein turnover (i.e. dysproteinemias). In addition, substances with low-molecular weight, such as uric acid and urea, strongly influence fructosamine levels.

Reports have shown that although fructosamine levels increase when diabetics with chronic kidney failure (CKD) undergo peritoneal dialysis (PD) and hemodialysis (HD), fructosamine is still a more reliable indicator of glycemic control than HbA1c in these conditions [[26]]. In addition, the concentration of fructosamine in patients may increase susceptibility to idiopathic infection [[3]]. Thus, fructosamine levels are too general a measure of glycated proteins to allow for reliable assessment of glycemic control [[27]].

2.2. Glycated albumin (GA)

Albumin makes up 60% of all proteins in serum with a concentration of 30–50 g/L [[28]]. Albumin's molecular weight is 66.7 kDa and it is composed of a single polypeptide chain with 585 amino acids and 17 disulfide chains (Figure 2). It also has 24 sites for the formation of AGEs and glycation occurs by non-enzymatic means [[29]]. Albumin is involved in biological homeostatic maintenance including osmotic pressure and blood pH. Albumin also binds free radicals, acts as an antioxidant, and transports a large number of solutes, such as low mass hormones, fatty acids, and drugs (e.g. Sudlow sites I and II are good places to connect with drugs) [[13]].



Graph: Figure 2. The crystal structure of albumin. The locations of the main drug binding sites in this protein are shown [[13]].

The glycation process has many effects on the structure of albumin that can alter its biological function [[31]]. The process of forming GA is divided into two main stages:

- **Stage I** : A reducing sugar, such as glucose, reacts with a primary amine group of a protein to form a reversible Schiff base. An Amadori product, which is more stable than a Schiff base, can subsequently be slowly formed.
- **Stage II** : Amadori products can undergo a series of reactions (oxidation, dehydration, and cross-linking) to form an intermediate compound (i.e. α-oxaloaldehydes such as glyoxal). These intermediate compounds react, to a greater extent than a reducing sugar, with lysine and arginine to create AGEs [[13]].

Diabetes clinical care and assessment of its pathophysiology necessitates the measurement of HbA1c and circulating concentration of AGEs. However, evidence suggests that glucose levels and the associated diabetic complications can vary markedly within each individual [[32]].

GA has been reported as a powerful indicator of glycemic control as the lifespan of GA (<1 month) is shorter than the current gold standard of HbA1c [[33]] and, as such, GA levels better represent variations in blood glucose concentrations over the span of a month. Thus, GA provides supplementary and valuable information for glycemic control in comparison to measured HbA1c levels.

2.3. Glycated hemoglobin A1c (HbA1c)

Hemoglobin A1 has various types, such as HbA1a, HbA1b, and HbA1c and is classified based on the different types of sugars attached to the proteins [[22]]. The lifespan of HbA1c is estimated to be about 90–120 days. Thus, it is known as an indicator of long-term glycemic control [[34]]. An elevated serum HbA1c (> 6.5%) is indicative of an irregular glycemic condition, whereas lower levels over three consecutive months (< 6.5%) reflects positive glycemic control [[40]]. Currently, the Federal Drug Association (FDA), the American Diabetes Association (ADA), and the Canadian Diabetes Association (CDA) accept HbA1c as an approved indicator for long-term glycemic control [[22], [36]]. However, HbA1c is not suitable for the assessment of a patient's glycemic status in certain disorders including hemoglobinopathies and disorders with abnormal red blood cell turnover. For example, numerous types of anemia erroneously change HbA1c levels [[37]]. All of these limitations to current approaches forced researchers to look for another indicator to evaluate glycemic control, especially over a shorter period of time [[34]]. GA was proposed as a new marker that, due to a shorter lifespan (12–21 days) [[34], [38]], can monitor a patient's glycemic control over 2–3 weeks [[13]].

3. GA assessment techniques and role in diabetes

There are many methods for measuring GA [[39]] including immunoassay-related techniques such as enzyme linked immunosorbent assays (ELISA) [[34], [40]], boronate affinity chromatography [[34], [41]], high-performance liquid chromatography (HPLC) [[42]], thiobarbituric acid (TBA) [[43]], and enzymatic methods [[44]]. In boronate affinity chromatography, an interaction occurs between sugar residues and a binding agent (e.g. phenylboronic acid) allowing for the separation of GA and non-GA [[13]]. Clinical methods measuring GA usually express results as a ratio of GA to total human serum albumin (HSA); therefore, these methods are not affected by changes in overall levels of HSA [[13], [27], [34]]. There are a number of assays used to measure GA that each have their own established normal ranges (Table 1). In this section, we review current and developing methods to assess GA and the biological impact of GA in diabetes.

Table 1. Normal range of GA by assay [46].

Method	Normal range (%)	Analyte	Reference
Enzyme-linked immunoassay	0.4–2.0		[40]
Radioimmunoassay	2.1–4.9b2.1–4.9[c]	Total or partial GAA	[47]
Enzyme-linked boronate immunoassay	3.4–7.2a3.4–7.2b		[42]
Boronate affinity chromatography	1.5–5.4		[48]
	6.8–10.3		[49]
Carboxymethyl cellulose ion exchange method	3.2–18.3b3.2–18.3a	ALB molecule	[50]
	9–15		[51]
Boronate affinity [HPLC]	13.9–18.3b13.9–18.3a		[52]
TBA method	3.9–12.7b3.9–12.7a	Total GAA	[53]
Enzymatic method	12.3–16.9		[54]

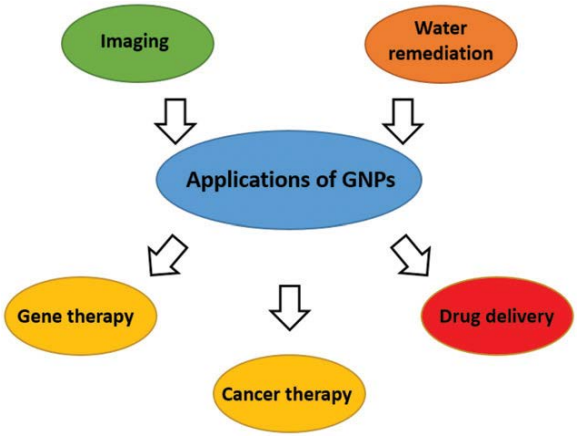
TBA: thiobarbituric acid; GAA: glycated amino acids; ALB: albumin.
a Calculated normal range (mean ±2 SD) from reported mean and SD.
b Calculated normal range (mean ±2 SD) from 0.53 ± 0.05 nmol/mg human serum albumin (mean ± SD).

Kohzuma et al. developed an enzymatic assessment of GA in 2011 (Lucica®GA-L, Asahi Kasei Pharma) [[49]], which involves the following steps:

- Elimination of endogenous glycated amino acids (GAA) and peroxide by ketoamine oxidase with peroxidase to form glucosone and amino acids.
- Hydrolysis of GAA to amino acid or peptide by an albumin-specific proteinase; Oxidation of GAA or peptide by ketoamine oxidase to glucosone, amino acids and the production of hydrogen peroxide. The hydrogen peroxide is measured quantitatively.
- Measurement of albumin concentration by the bromocresol purple (BCP) method [[54]].
- Finally, calculation of % GA levels relative to total albumin.

The biological impact of GA is partly demonstrated by assessment of non-enzymatic glycation of albumin performed using quartz crystal microbalance with dissipation monitoring (QCM-D). QCM consists of a thin piezoelectric plate, which has acoustic resonances in the MHz range. When the crystal comes into contact with the sample, the resonance parameters change. Heller et al. utilized QCM-D to investigate the effect of glycation by glucose and glyoxal on HSA's binding affinity for hemin [[55]]. Glycation of albumin by an intermediate glycosylation compound, such as glyoxal, leads to glycation of arginine residues on HSA producing AGE. Interestingly, glyoxal content in blood is increased with diabetes [[55]]. Non-enzymatic glycation of HSA by glyoxal, but not glucose, reduced the binding of hemin to HSA [[62]]. Thus, AGE formation significantly reduces the biological efficacy of HSA.

A developing therapy for diabetics that are at risk of extensive AGE formation is gold nanoparticles (GNPs). GNPs are among the most commonly used nanostructures in biomedical, industrial, and environmental applications. GNPs have been used for therapeutic applications (Figure 3), such as in chronic lymphocytic leukemia, as they increase drug efficacy due to their biocompatibility, high surface area, and surface functionalization [[56]]. Seneviratne et al. examined non-enzymatic glycation of HSA using GNPs [[56]]. The aim of this study was to evaluate the rate of AGE formation in the presence of varied concentrations of 2 nm GNP (2GNP) and to analyze the glycation of HSA related AGE. Analytical studies were performed with protein mixtures containing 2GNP in order to estimate the correlation between UV absorbance and the secondary structure of HSA. 2GNP was found to produce a substantial reduction in non-enzymatic reactivity between GA and HSA which results in less AGE formation. Thus, GNP may provide a therapeutic option to lower AGE in diabetics.



Graph: Figure 3. Various applications of GNPs.

4. Relationship between indicators of glycemic control and their predictive ability

Recent clinical evidence has shown the favorable effects of strict glycemic control on cardiovascular disease, which is one of the leading causes of death in diabetes [[59]]. Strict glycemic control is often illustrated by HbA1c, since in DM the hemoglobin level is one of the most important diagnostic factors [[61]]. HbA1c reflects glycemic status over a relatively long period (3–4 months), but does not accurately reflect glycemic control under conditions with rapid changes in glycemia [[69]]. HbA1c had been thought appropriate to select suitable therapies for patients with DM [[62]], however HbA1c is not suitable to determine glycemic control in all diabetic patients due in part to conditions in which HbA1c levels are excessively high or low (Table 2) [[64]], and in situations such as hemoglobinopathy in which there are changes to erythrocyte lifespan [[67]]. In these conditions, GA is generally determined to be a more appropriate measurement of glycemic control.

Table 2. Medical conditions with altered HbA1c levels [68].

1. Conditions with abnormally high HbA1c levels
1.1 Rapid improvement of glycemic control
1.2 Iron deficiency anemia
1.3 Pregnancy
1.4 Variant Hemoglobin
2. Conditions with abnormally low HbA1c levels
2.1 Rapid deterioration of glycemic control
2.2 Diseases with shortened lifespan of red blood cells
2.2.1 Hemolytic anemia, hemorrhage, liver cirrhosis
2.2.2 Chronic kidney disease (renal anemia)
2.2.3 During treatment of iron deficiency anemia
2.3 Variant hemoglobin
2.4 Neonates, neonatal diabetes mellitus
2.5 Hereditary Persistence of Fetal hemoglobin (HBFH)

GA is often assessed by the Lucica GA-L enzymatic method in which GA is hydrolyzed by albumin-specific proteinases to amino acids and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which is measured quantitatively. The GA value is calculated as a percentage relative to total albumin and is measured by bromocresolpurple (BCP). The advantage of this technique is that it prevents interference with endogenous glycated amino acids [[69]]. HbA1c is often assessed by routine HPLC, which has been standardized according to The Japan Diabetes Society [[70]]. Several groups have compared enzymatic assessment of GA (Lucica®GA-L, Asahi Kasei Pharma), HPLC assessment of HbA1c, and GA:HbA1c to determine the most appropriate measurement of glycemic status in diabetics with different complications. Here we review the most appropriate indicator of glycemic status for: (a) conditions with high HbA1c, (b) conditions with low HbA1c, and (c) T1D subtypes. In addition, the relationship between indicators of glycemic status and severity of CAD is also reviewed.

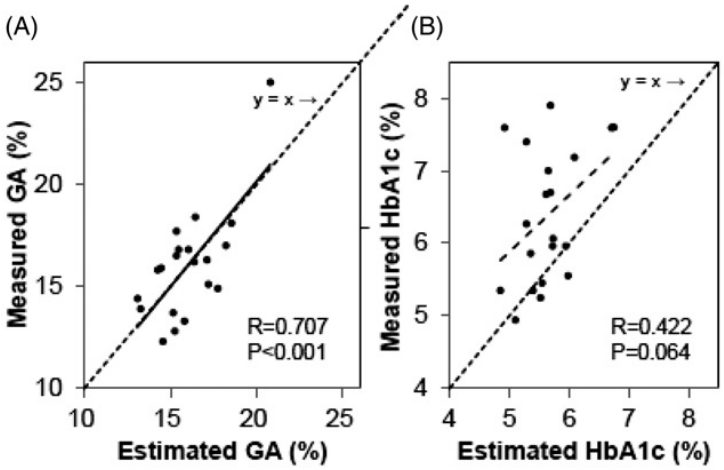
4.1 Conditions with abnormally high HbA1c levels

Iron deficiency anemia

It is known that low HbA1c levels are observed in most types of anemia but that high HbA1c levels are observed in iron deficiency anemia [[71]]. In situations with high HbA1c, such as iron deficiency anemia, a formula to estimate HbA1c levels has been developed. Inoue et al. sought to define an equation to extrapolate HbA1c (eHbA1c) from the GA value [[73]]. A total of 248 data sets from the 731 patients (including non-diabetes

patients), without altered metabolism of hemoglobin or albumin, which had HbA1c and GA values measured simultaneously were analyzed. The correlation between HbA1c and GA was assessed and the authors successfully developed an equation for calculating eHbA1c to evaluate the glycemic control of patients with altered hemoglobin metabolism.

The influence of iron deficiency on the relationship between GA and HbA1c to glycemic control was investigated by Moriya et al. in pregnant diabetic women [[74]]. 20 women with diabetes were selected (7 with T1D and 13 with T2D). There was no significant association between GA and HbA1c or GA and estimated GA (eGA), however, the HbA1c was significantly higher than the eHbA1c (Figure 4). Other studies investigating GA and HbA1c in different types of anemia have found that high GA:HbA1c occurs in anemic neonates and infants [[75]], chronic renal failure (renal anemia) [[77]], hemolytic anemia [[78]], and persistant fetal hemoglobin, while HbA1c is low. As mentioned before, iron deficiency anemia that is associated with high levels of HbA1c and low GA/HbA1c ratios have been reported [[79]]. Diseases that are associated with high or low GA/HbA1c ratios are summarized in Table 3. In summary, GA is a more appropriate indicator than HbA1c of glycemic control in diabetic patients with iron deficiency anemia [[79], [81]].



Graph: Figure 4. Relationship between the measured values and the estimated values for GA (A) and HbA1c (B) in 20 pregnant women with diabetes [[76]].

Table 3. Diseases and conditions with high/low GA/HbA1c ratios [68].

Diseases with high GA/HbA1c ratios	Diseases with low GA/HbA1c ratios
Rapid deterioration of glycemic control	Rapid improvement of glycemic control
At the time of onset of fulminant type 1 DM	Iron deficiency anemia
	Pregnancy
At the time of onset of acute-onset type 1 DM	Nephrotic syndrome
	Hyperthyroidism
Hemolytic anemia	Administration of glucocorticoids
During treatment of iron or erythropoietin	Cushing's syndrome
Liver cirrhosis	Obesity, smoking
Chronic kidney disease (renal anemia)	Hyperuricemia, hypertriglyceridemia
Neonates/infants, neonatal DM	Nonalcoholic fatty liver (NAFLD) with high
Hereditary persistence of fetal hemoglobin (HPFH)	ALT[a]: levels
Hypothyroidism	Administration of drug for postprandial plasma glucose
Adrenal insufficiency	

Emaciation	
Postprandial hyperglycemia/large glycemic excursion	Variant hemoglobin
Diseases with high or low GA/HbA1c ratios	
Type 1 DM	Variant hemoglobin
Postgastrectomy	Diabetic nephropathy stage 4
	Nonalcoholic steatohepatitis (NASH)

4 *ALT*[a]: Alanine aminotransferase.

Pregnancy

Many pregnant women suffer from iron deficiency in the third trimester. Studies have shown that iron deficiency increases HbA1c levels [[82]]. According to these results, the Japanese Society of Diabetes and Pregnancy recommends GA be assessed to help prevent perinatal complications in mothers, fetuses, and neonates [[84]].

Variant hemoglobin

Many reports explain that low HbA1c levels are observed in variant hemoglobin; however, some studies report high levels of HbA1c [[85]]. In this disorder, HbA1c is influenced by many factors that do not affect GA levels [[82]]. Thus, GA is a more accurate marker than HbA1c for glycemic control in diabetic patients with variant hemoglobin [[68]].

4.2 Conditions with abnormally low HbA1c levels

Diseases with shortened lifespan of red blood cells

Hemolytic anemia, hemorrhage, liver cirrhosis

Hemolytic anemia is associated with reductions in HbA1c [[88]]. Anemia increases the synthesis of red blood cells (RBCs) and the lifespan of RBCs. As a result, HbA1c levels are decreased [[90]]. However, it has been shown that GA levels accurately reflect glycemic control in hemolytic anemia because GA is unaffected by RBC lifespan [[78]].

Liver cirrhosis is another disorder in which RBCs have a shortened lifespan and thus HbA1c levels are decreased [[91]]. High levels of GA are observed in liver cirrhosis due to the long lifespan of albumin [[92]]. Thus, neither HbA1c nor GA can be used alone as a glycemic control indicator in this disorder [[68]].

Chronic kidney disease (renal anemia)

Erythropoietin treatment, and blood loss during HD of patients with chronic kidney disease (CKD) leads to significantly reduced levels of hemoglobin [[33], [93]]. Masaaki et al. investigated the usefulness of GA and HbA1c at determining glycemic control in diabetics undergoing HD, taking into account erythropoietin injections [[93]]. The presence of CKD altered the correlation between HbA1c and average PC, but did not alter the correlation between GA and average PG. Thus, HbA1c levels are likely altered in CKD and therefore GA is more representative of true glycemic control in diabetics with CKD. Also, GA correlated better than HbA1c with a number of indicators of coronary artery disease (CAD) severity. Therefore, GA is better than HbA1c for determination of the degree of CAD progression in patients with T2D (Please refer to coronary artery disease (CAD) under section 4.4).

CKD patients can also be treated with PD in place of HD. Lee et al. investigated the most suitable indicator of glycemic control in CKD patients undergoing PD [[94]]. Since HbA1c levels are affected by uremia [[66], [95]] and anemia [[96]], HbA1c may not be a good marker for CKD patients undergoing PD. Alternative indicators of glycemic control include GA [[97]], albumin-corrected fructosamine (AlbF) [[24]] and fructosamine [[98]]. 25 T2D patients were selected to undergo maintenance PD for more than three months. Interstitial fluid (ISF) glucose

levels were measured by a continuous glucose monitoring system (CGMS) every five minutes over three days. The correlation between ISF glucose and GA (r = 0.26) was not as strong as HbA1c (r = 0.51) and AlbF (r = 0.54). Thus, HbA1c and AlbF were determined to be good indicators of glycemic control in diabetic patients with CKD undergoing PD.

In addition to determining glycemic control, indicators of glycemic control may also predict future complications. Hasslacher et al. studied 380 T2D patients with healthy kidney function or moderate renal dysfunction (CKD stages 1–3) for almost five years [[123]]. GA and HbA1c correlated well and were not dependent upon gender, age, renal function or anemia. While there was no association between either GA or HbA1c and cardiovascular or cerebrovascular events, high HbA1c and high GA were indicative of increased risk of peripheral vascular and renal events respectively. It is unclear whether high GA is detrimental to the glomerulus or is more sensitive to postprandial hyperglycemic events.

The predictive ability of HbA1c and GA at determining retinopathy, nephropathy, and cardiovascular outcomes in T1D was studied by Nathan et al. in the Diabetes Control and Complications Trial followed by the Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC) [[99]]. The DCCT showed that reducing HbA1c levels reduced the risk of microvascular complications which persisted during the EDIC study [[62], [100]]. Data from 497 patients from the DCCT was studied and it was determined that both HbA1c and GA were predictive of retinopathy and nephropathy, yet only HbA1c correlated with cardiovascular disease. Thus, GA and HbA1c can provide information regarding risk of future complications in T1D.

During treatment of iron deficiency anemia

It is known that low HbA1c levels are observed in most types of anemia, but that high HbA1c levels are observed in iron deficiency anemia [[71]]. Therefore, the level of GA can be a more appropriate scale for glycemic control in diabetic patients with iron deficiency anemia [[79], [81]].

Variant hemoglobin

Please refer to Variant Hemoglobin under section 4.1. As detailed in section 4.1 above, variant hemoglobin can cause both increases and decreases in hemoglobin levels.

Neonatal diabetes mellitus

The suitability of GA and HbA1c as markers of glycemic control in patients with neonatal DM (NDM) has been investigated by Suzuki and Koga [[76]]. Due to the high level of fetal hemoglobin (HbF) in patients with NDM, albumin levels are not reliable as an indicator of glycemic control [[101]]. Five patients with a mean age of 38 years old were studied and GA, HbF and HbA1c levels were measured monthly over six months. It was reported that GA could be a useful indicator of glycemic control in patients with NDM; however, many more patients with NDM need to be examined for confirmation of this result.

Hereditary persistence of fetal hemoglobin (HPFH)

Fetal hemoglobin or fetal hemoglobin (also hemoglobin F, HbF or $\alpha 2\gamma 2$) is found in the human fetus and acts as the main oxygen transporter to the newborn during the last seven months of fetal development and remains until the newborn is roughly six months old. Fetal hemoglobin's main benefit is that it is able to bind to oxygen with a much greater affinity than adult hemoglobin allowing tissues to be more readily supplied with oxygen. Moreover, the fetus is able to have greater access to oxygen from the mother's bloodstream. By the time the newborn is six months old, adult hemoglobin has completely replaced fetal hemoglobin. Certain cases such as thalassemia have caused delay in cessation of HbF production until 3–5 years of age. However, when an individual is an adult, adult hemoglobin is able to reactivate pharmacologically providing treatment to those who have sickle-cell disease [[103]].

HPFH is a mild condition in which notable fetal hemoglobin generation proceeds well into adulthood, slighting the ordinary shutoff point after which just adult-type hemoglobin should be generated [[104]].

4.3 T1D subtypes

Matsumoto et al. investigated the usefulness of GA:HbA1c versus HbA1c at determining glycemic control in subtypes (acute-onset classical type 1 A, fulminant, and slowly progressive type 1) of T1D [[100]]. In all, 56 patients (43 females and 13 males) with T1D were assessed for HbA1c, GA and postprandial serum C-peptide immunoreactivity (CPR). HbA1c, GA, and GA:HbA1c correlated with some parameters of daily glucose profile in study patients (Table 4). In fulminant T1D, GA:HbA1c was significantly higher than in slowly progressive T1D and GA:HbA1c correlated with the mean amplitude of glucose excursion (MAGE). Lastly, in all T1D GA and GA:HbA1c correlated with MAGE. Thus, GA:HbA1c is a sensitive indicator of glycemic control in T1D, especially the fulminant subtype.

Table 4. Relationship between HbA1c, GA, GA: HbA1c ratio and parameters of daily glucose profile in study patients [105].

		Univariate	Multivariate (model 1)	Multivariate (model 2)			
Factors	Parameters	R	P	F	P	F	P
	FBG	0.037	NS				
	MBG	0.467	<0.001	2.21	NE	089	NE
	MaxBG	0.572	<0.001	1.23	NE		
GA	MAGE	0.585	<0.001	27.53	<0.001	0.13	NE
	Delta BG	0.628	<0.001			34.60	<0.001
	FBG	0.032	NS				
	MBG	0.447	<0.001	0.68	NE	2.37	NE
HbA1c	MaxBG	0.480	<0.001	15.87	<0.001		>0.001
	MAGE	0.421	<0.001	0.01	NE	1.69	
	Delta BG	0.494	<0.001			17.11	
	FBG	0.113	NS				
	MBG	0.200	NS				
GA:HbA1c	MaxBG	0.343	0.010	0.62	NE		
	MAGE	0.444	<0.001	13.02	<0.001	13.02	<0.001
	Delta BG	0.422	0.001			1.12	NE

5 GA: Glycated albumin; FBG: Fasting blood glucose; MBG: Mean blood glucose; MaxBG: Maximum blood glucose; Delta BG: Maximum–Minimum blood glucose; MAGE: Mean amplitude of glucose excursions; GA:HbA1c: ratio of GA to HbA1c; NE: not entered.

Despite reports in T2D patients, the DCCT/EDIC study found no significant relationship between GA and cardiovascular events in subjects with T1D [[99]]. Similarly, in 2014 Kim et al. reported that GA:HbA1c might not be associated with carotid atherosclerosis in patients with T1D [135]. Carotid intima media thickness (IMT), GA, HbA1c, body mass index (BMI) and waist ratio were compared. Waist circumference, IMT and BMI were lower in Group I (subjects with GA:HbA1c ≥2.90) than in Group II (subjects with GA:HbA1c <2.90). These results show, contrary to what has been demonstrated in patients with T2D, no significant relationship between IMT and GA:HbA1c for T1D patients.

4.4 Prediction of CAD severity using indicators of glycemic status

Recently there has been much interest into using an indicator of glycemic status to predict severity of coronary artery disease (CAD). Shen et al. studied T2D patients and compared the value of serum GA to HbA1c in order to

assess the presence and severity of CAD [[106]]. GA and HbA1c were measured in 829 T2D patients of whom 664 had significant CAD (240 with 1-vessel disease, 207 with 2-vessel disease, and 217 with 3-vessel disease). Diabetic patients with pronounced CAD had greater serum GA, but not HbA1c, levels. GA also correlated better than HbA1c with a number of indicators of CAD severity. Thus, GA is superior to HbA1c for determination of degree of CAD progression in patients with T2D. Many studies conducted on Japanese patients with T2D also suggest that GA is better than HbA1c at determining the degree of CAD progression [[106]], however, Ikeda et al. [[108]] indicated that 1,5-anhydroglucitol (1,5-AG) is superior to HbA1c as an indicator of CAD progression in Japanese T2D patients. 1,5-Anhydroglucitol, also known as 1,5-AG, is a six-carbon chain monosaccharide derived from ingestion of food. The body is unable to process this monosaccharide and it is different in structure from glucose. 1,5-AG competes with glucose for reabsorption into the kidneys. When glucose levels rise, 1,5-AG is excreted through the urine and levels of 1,5-AG fall. Therefore, 1,5-AG is inversely related to hyperglycemia and may be a useful indicator for measuring blood sugar abnormalities in diabetics [[109]]. Conversely, Ma et al. assessed GA, HbA1c, and 1,5-AG, and degree of CAD severity in 272 (178 men and 94 women) Chinese CAD patients [[110]]. In this study, GA correlated better with CAD severity, than HbA1c and 1,5-AG, in those at high risk of CAD.

Ma et al. determined the relationship between HbA1c and GA in atherosclerotic middle-aged and elderly Chinese patients with impaired glucose regulation (IGR) [[111]]. They studied atherosclerotic middle-aged and elderly Chinese patients' IGR and compared the value of serum GA to HbA1c. 640 participants were recruited and it was found that both GA and HbA1c are appropriate parameters for detection of an increased risk of subclinical atherosclerosis among middle-aged and elderly Chinese with IGR. Thus, it is unclear what the most appropriate glycation indicator is to determine CAD severity.

4.5 Prediction of β-cell function using indicators of glycemic status

Saisho et al. reported that lower β-cell function was associated with a higher GA:HbA1c in T2D Japanese patients [[112]]. The purpose of this research was to find the logical relationship between baseline β-cell functionality and GA:HbA1c in T2D. In this study, 210 patients were evaluated and baseline β-cell function was investigated by postprandial C-peptide immunoreactivity index (PCPRI). There was a strong correlation between the baseline and the 2 year GA:HbA1c, even though the HbA1c level recovered. In addition, lower PCPRI correlated independently with a higher baseline GA:HbA1c after 2 years.

Lee et al. investigated the suitability of various indicators of glycemic status at determining β-cell function in childhood diabetes [[113]]. 137 patients (3–18 years; 63 males, 74 females) with T1D and T2D were recruited. They measured the ratio of estimated average glucose to FPG (eAG:fPG), GA, HbA1c, and fructosamine. Also, the homeostasis model evaluation of β-cell function (HOMA-β) was determined. They found that HOMA-β and eAG:fPG were positively correlated, while HOMA-β and the GA:HbA1c were negatively correlated. eAG:fPG related more closely to the levels of HOMA-β and CRP than GA:HbA1c. Also, the measurement accuracy of eAG:fPG was better than that of GA:HbA1c for diagnosing HOMA-β. Thus, eAG:fPG is superior to GA, HbA1c, fructosamine, and GA:HbA1c for assessing β-cell function in childhood diabetes [[113]]. Certain co-morbidities cause fluctuations in GA and HbA1c values. For instance, low HbA1c and a high GA:HbA1c have been reported in most patients with variant hemoglobin, resulting from amino acid mutations, and, in some cases, vice versa [[85]]. In various conditions, such as nephrotic syndrome [[77]], administration of glucocorticoids [[114]], Cushing's syndrome [[115]], and smoking [[116]] low GA and low GA:HbA1c are observed. Low HbA1c and high GA levels (high GA:HbA1c) are also reported in liver cirrhosis cases [[117]]. The diseases and conditions in which it is appropriate to assess glycemic control with GA are summarized in Table 5. In addition, the importance of measuring postprandial blood glucose (PPG) has been noted by several epidemiologic studies, such as the Funagata Study [[115]], the Diabetes Intervention Study (DIS) [[116]], and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe Study (DECODE) [[117]]. Sakuma et al. studied the ability

of fasting blood glucose (FBG) and postprandial blood glucose (PPG) to predict HbA1c and GA [[114]]. 51 patients with T2D who had a less than a 1% change in HbA1c levels over the last four months were recruited and GA and HbA1c were measured simultaneously. GA and HbA1c were deemed to be predictable by FBG and PPG, respectively. Thus, if GA is the most suitable indicator of glycemic control in a number of diabetic conditions, then PPG should be used over FBG when GA measurement is unavailable.

Table 5. Diseases in which measurement of GA is desirable [68].

Hematologic disorders	Conditions in which glycemia improves rapidly
Hemolytic anemia	Rapid improvement of glycemic control
Hemorrhage	Conditions in which glycemia deteriorates rapidly
Iron deficiency anemia	Rapid deterioration of glycemic control
Premenopausal women	At the time of onset of fulminant type 1 DM
Pregnancy	At the time of onset of acute-onset type 1 DM
During treatment of iron deficiency anemia	Postprandial hyperglycemia
Liver cirrhosis	Administration of drug for postprandial plasma glucose
Renal anemia	Type 1 DM
Variant hemoglobin	Postgastrectomy
Neonates/infants, neonatal DM	
Hereditary persistence of fetal hemoglobin (HPFH)	

5. Concerns regarding GA as a marker for glycemic control

As reviewed here, GA levels are not affected by anemia, chronic kidney disease, pregnancy, or variant hemoglobin; however, abnormally low levels of GA can occur in some situations including infancy [[118]], hyperthyroidism, [[120]] and nephrotic syndrome [[77], [121]], while abnormally high levels of GA occur can occur in liver cirrhosis [[92]] and hypothyroidism [[120]]. In addition, there is a close relationship between GA and BMI such that GA levels are low in obese individuals and high in lean individuals [[122]]. Studies have also shown that there is a substantial negative correlation between BMI and CRP [[122]]. Moreover, a similar relationship has been observed between GA and CPR [[124]]. Therefore, in obese people, patients with hyperuricemia and smokers, GA levels should be compared to plasma glucose levels [[68]].

6. Conclusion

Adequate glycemic control and early diagnosis are critical to diabetes care. Since hyperglycemia increases the risk of kidney disease, heart disease and stroke, lower limb amputations and blindness [[14]] and it is expected that the number of diabetic patients worldwide will reach 552 million by 2030 [[1]], appropriate diabetes care will greatly improve health outcomes for people worldwide and save significant health care costs.

Blood glycated proteins represent glycemic control and have been proposed as a useful tool for the diagnosis of diabetes, determination of adequate diabetes care, and even determination of comorbidity risk including CAD, nephropathy, and neuropathy. While HbA1c indicates glycemic control status over a relatively long period, it does not reflect glycemic control accurately under conditions with rapid changes in the lifespan of red blood cells. In addition, it is known that in hematologic disorders (such as anemia and variant hemoglobin), abnormal HbA1c levels are observed. GA, which is not influenced by changes in the lifespan of erythrocytes, is thought to be an alternative indicator for glycemic control in diabetic patients, however, in some situations, the level of GA is abnormal and thus HbA1c can be a better tool in these situations. There are health conditions in which it is unclear which glycated protein is most appropriate for diagnosis of diabetes, determination of adequate

diabetes care, and determination of comorbidity risk. These discrepancies may be due to patient genetic background, type of diabetes and severity of diabetes or comorbidity. It is important for clinicians to be aware of situations in which glycated proteins, such as HbA1c and GA, are altered and thus are not appropriate measures of glucose excursions.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

- Abbreviations
- DM Diabetes Mellitus
- FPG fasting plasma glucose level
- HbA1c 2-h plasma glucose (2HP), Hemoglobin A1c
- GA glycated albumin
- HPLC: High-performance liquid chromatography
- HPFH Hereditary Persistence of Fetal hemoglobin
- T1D Type 1 diabetes
- T2D Type 2 diabetes
- AGE glycation end product
- FN3K Fructosamine-3-kinase
- FL3P fructoselysin-3-phosphate
- CKD chronic kidney failure
- PD peritoneal dialysis
- HD hemodialysis
- FDA Federal Drug Association
- ADA American Diabetes Association
- CDA Canadian Diabetes Association; E
- LISA enzyme linked immunosorbent assays
- HPLC high-performance liquid chromatography
- TBA thiobarbituric acid
- HSA human serum albumin
- GAA glycated amino acids
- ALB albumin
- BCP bromocresol purple

- QCM quartz crystal microbalance
- QCM-D quartz crystal microbalance with dissipation monitoring
- GNP gold nanoparticles
- eHbA1c extrapolated HbA1c
- ALT Alanine aminotransferase
- NAFLD Nonalcoholic fatty liver
- NASH Nonalcoholic steatohepatitis
- RBC red blood cell
- CAD coronary artery disease
- AlbF albumin-corrected fructosamine
- ISF Interstitial fluid
- CGMS continuous glucose monitoring system
- DCCT The Diabetes Control and Complications Trial
- EDIC Epidemiology of Diabetes Interventions and Complications study
- NDM neonatal DM
- HbF fetal hemoglobin
- CPR C-peptide immunoreactivity
- MAGE Mean amplitude of glucose excursion
- FBG Fasting blood glucose
- MBG Mean blood glucose

Footnotes

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