

# Introduction of glycated albumin in clinical practice

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**Abstract:** Glycated albumin (GA) is the result of non-enzymatic glycation of albumin that occurs into circulation. Glycation rate of albumin depends on glycemia and on the time of albumin stay into the bloodstream, so GA has been proposed as a biomarker of glycemic status. Consequently, several studies investigated the clinical usefulness of GA in diabetes, showing that it has good diagnostic accuracy and it could represent a useful screening test. Additionally, due to the shorter lifespan of albumin in comparison to the traditional biomarkers of glycemic control, like HbA1c, GA can be considered a biomarker of early response to hypoglycemic treatment. Moreover, GA has been proposed as a biomarker of glycemic control in patients with diabetic nephropathy, anemia, pregnancy, haemoglobin variants, transfusions, especially when HbA1c loses its accuracy. Notably, recent findings have associated GA also with the progression of diabetes over microangiopathy, such as retinopathy and nephropathy, and cardiovascular outcomes. GA circulating levels increase modestly with age in healthy subjects, and are influenced by conditions altering albumin turnover such as hypo- and hyperthyroidism, cirrhosis, nephrotic syndrome, obesity. The introduction of GA in clinical practice is facilitated by the establishment of GA reference intervals, recently described in several studies with comparable results, and the knowledge of the biological determinants of its circulating levels.

**Keywords:** Glycosylated serum albumin; glycated haemoglobin A; hyperglycemia; biomarkers; hypoglycemic agents

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## Non-enzymatic glycation of albumin

Non-enzymatic glycation consists in the addition of a carbonyl compound to an amino group of a peptide or a protein leading to the formation of stable advanced glycation end products (AGEs). Glycolytic intermediates, reducing sugars and their derivatives can all undergo to glycation. Among them, glucose is the most abundant in blood. The amino groups involved in the glycation process are lysine residues, N-terminal amino groups, and the guanidine group of arginine. It seems that also cysteine and tryptophan can undergo glycation but this process is less characterized (1). Glycation is a multi-step process that proceeds through initial reversible steps and leads to the formation of stable glycation products. The early steps consist in the reversible

condensation of the carbonyl compound and the amino group with the formation of a Schiff's base. This reaction proceeds very slowly and leads to the rearrangement of the Schiff's base to form an Amadori product, a more stable ketoamine. The next steps involve several rearrangements that lead to a large panel of compounds, generally known as AGEs (2). While the first stages are reversible and relatively fast, the formation of more stable AGEs requires days or weeks, so many proteins with short half-lives could be degraded before AGEs accumulation can occur. The interest in the comprehension of these mechanisms has raised exponentially in the last decades because they represent the pathophysiological link between hyperglycemia and the vascular damage that underlies the clinical complications of diabetes. Non-enzymatic

**Table 1** Summary of the clinical studies evaluating glycated albumin for diabetes diagnosis

Authors	Definition of diabetes	Number of participants	Diabetes prevalence, n (%)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-off
Furusyo <i>et al.</i> (14)	HbA1c >48 mmol/mol and/or FPG >7 mmol/L	1,575	72 (4.6%)	0.91 (n.a.)	83.3% (n.a.)	83.3% (n.a.)	15.5%
Ikezaki <i>et al.</i> (16)	2hPG >11.1 mmol/L	176	29 (16.5%)	0.67 (0.54–0.78)	62.1% (n.a.)	61.9% (n.a.)	15.2%
Wu <i>et al.</i> (17)	2hPG >11.1 mmol/L	1,559	132 (8.5%)	0.86 (0.82–0.90)	74% (n.a.)	85% (n.a.)	15%
Ma <i>et al.</i> (19)	2hPG >11.1 mmol/L	1,971	755 (38.3%)	0.83 (0.81–0.85)	76.8% (73.6–79.7%)	76.8% (74.4–79.2%)	17.1%
Hsu <i>et al.</i> (20)	History of diabetes	2,192 (1,188 cases, 1,004 controls)	n.a.	0.86 (n.a.)	78.5% (n.a.)	80% (n.a.)	14.9%
Bellia <i>et al.</i> (18)	HbA1c >48 mmol/mol	334	18 (5.4%)	0.80 (0.75–0.84)	72.2% (46.5–90.3%)	71.8% (66.5–76.7%)	14%
Zemlin <i>et al.</i> (23)	2hPG >11.1 mmol/L	1,294	94 (7.3%)	0.87 (0.78–0.89)	64.8% (54.1–75.6%)	93.5% (92.0–94.9%)	14.9%

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; n.a., not available; 2hPG, plasma glucose after 2 h during an oral glucose tolerance test.

glycation represents also the way to “produce” *in vivo* biomarkers of hyperglycemia, due to the observation that its rate depends on glucose concentration in blood, assuming the concentration of proteins to be constant. The most well-described glyceic biomarker arising from non-enzymatic glycation is glycated haemoglobin, and particularly the isoform A1c (HbA1c) (3). Nevertheless, other biomarkers have been proposed next to, and beyond, HbA1c (4).

Albumin contains 585 residues including 59 lysine residues that can, potentially, undergo glycation. The main glycation site in mature albumin is Lys-525, accounting for about 33% of the overall glycosylation of albumin. Albumin contains also 24 arginines that can undergo glycation. Nevertheless, the susceptibility of these residues to glycation is highly variable, depending on local acid-basic catalysis effect, the accessibility of the site, the local  $pK_a$  at each site (5,6). As a result, the term “glycated albumin” (GA) includes a large spectrum of molecular species arising from different glycation patterns of albumin, influencing the accuracy of some analytical methods for GA determination.

Notably, glycation of albumin can affect its ability to bind several compounds, including fatty acids, hormones, and drugs (7–10). Albumin half-life is approximately 2–3 weeks, which is enough to allow the formation of advanced, stable glycation end products. Among all plasma proteins, albumin and immunoglobulin G are the most abundant accounting together for about 70% of all plasma proteins. Physiologically, albumin is present at the

concentration of 35–45 g/L. Due to the high concentration of albumin and glucose in blood in comparison to other plasma protein and carbonyl compounds, respectively, GA is very sensitive to the variation of plasma glucose, representing a useful biomarker for the evaluation of glyceic homeostasis. Utility of GA has been demonstrated in several clinical scenarios, including screening and diagnosis of diabetes, short-term monitoring of hypoglycemic treatment and diabetes progression (11,12). Specifically, the use of GA seems to be particularly promising in iron deficiency anemia, pregnancy, chronic kidney disease (CKD), and other conditions in which HbA1c is less accurate in estimating glyceic control (13).

### Use of GA for diabetes diagnosis

A large body of evidence has documented that GA is a reliable biomarker for the diagnosis of diabetes (14–18). Some studies have also compared the diagnostic accuracy of GA in relation to the traditional glyceic metrics routinely used for diabetes diagnosis, finding that GA could be helpful for clinicians especially when a discrepancy between traditional biomarkers is observed reducing the rate of missed diagnosis (19–24). Overall, GA has a good diagnostic accuracy for the diagnosis of diabetes, with area under the curve (AUC) ranging from 0.67 to 0.91 (Table 1).

A large population-based cohort study including more than 1,500 subjects from Japan documented that GA was

able to identify subjects with diabetes with high accuracy (AUC: 0.91) at the cut-off of 15.5%. Notably, definition of diabetes was based on Fasting Plasma Glucose (FPG) and HbA1c only, so a significant number of diagnosis based on 2h-plasma glucose (2hPG) after an oral glucose tolerance test (OGTT) could be missed (14). Nevertheless, the study provided significant insights on the usefulness of GA as a screening tool for diabetes. The use of GA as a diagnostic test has been investigated also in the study of Ikezaki *et al.*, who documented that GA was able to identify newly diagnosed diabetics, with comparable accuracy than HbA1c (AUC: 0.64 *vs.* 0.701, respectively;  $P=0.157$  for the comparison) (16). Hwang *et al.* used a different approach to calculate the optimal cut-off of GA for the diagnosis of diabetes, calculating linear regression models based on FPG and 2hPG in a retrospective analysis and identifying the value of 14.3% as the best cut-off for diabetes diagnosis (15). When the authors compared the diagnostic performance of GA with the ones of HbA1c, GA showed higher sensitivity, but lower specificity than HbA1c. In the Taiwan Lifestyle Study, a large community-based cohort study, the AUC of serum GA for the diagnosis of diabetes defined by 2hPG was 0.86, with an optimal cut-off of 15% (17). Notably, the authors found that the combined use of GA and FPG would reduce the frequency of OGTT by 22.5%, without affecting the overall diagnostic accuracy. Ma *et al.* found similar AUC values in a Chinese study involving 1,971 outpatients undergoing an OGTT. Authors also showed that the ability to identify newly diagnosed patients was lower for GA in comparison to FPG when the two biomarkers were considered separately, but the overall diagnostic accuracy significantly increased when they were used in combination, reaching a sensitivity of 92% and a specificity of 77% (19). In a large case-control study performed in Taiwan, Hsu *et al.* evaluated the ability of GA to discriminate between subjects with previously diagnosed diabetes and healthy volunteers selected on the basis of FPG, HbA1c and no treatment for diabetes. The authors found that GA values higher than 14.9% detected diabetes with an AUC of 0.86 (20). Interestingly, He *et al.* evaluated the role of GA in supporting the diagnosis of diabetes when biochemical and clinical findings were ambiguous, namely for asymptomatic subjects with FPG >7 mmol/L undergoing OGTT. The authors found that repeated FPG and/or HbA1c, without performing an OGTT, would result in 14.31% of missed diagnosis, and that the introduction of GA in the diagnostic workup would significantly reduce the rate of missed diagnosis (9.48%) (24).

Although the vast majority of the studies investigating the use of GA for diabetes screening and diagnosis were performed in Asian populations, recently this clinical application of GA has been tested also in different ethnicity. In an Italian study, Bellia *et al.* documented the clinical usefulness of GA for diagnosing diabetes in a Caucasian population of subjects at risk for diabetes (AUC: 0.80; 95% CI: 0.75–0.84;  $P<0.0001$ ) with an optimal cut-off of 14% based on the equilibrium between sensitivity and specificity (18). In the study of Zemlin *et al.*, GA showed a very high specificity of GA for newly diagnosed diabetes in a large, mixed ancestry South African population. When GA was compared to HbA1c, the former was less sensitive than HbA1c, but significantly more specific. It should be noticed that the mean body mass index (BMI) of the subjects included in the study was 28.7, indicating that a significant percentage of them were overweight or obese. Indeed, a significant negative correlation between GA and BMI has been documented by several studies (17,25). Accordingly, the authors concluded that clinical usefulness of GA should be reassessed in non-obese subjects, also in comparison to the traditional measures of hyperglycemia (23). In the Africans in America Study, Sumner *et al.* evaluated the ability of GA and other glycemic measures to detect prediabetes in subjects of African ancestry living in America, finding that GA, in combination with HbA1c, would identify a significant percentage of people with diabetes not detected by HbA1c alone. Again, due to the influence of BMI on GA, results were more significant when only non-obese subjects were considered (21,26).

Overall, these findings showed that GA could be a reliable biomarker for diabetes screening and diagnosis, although its contribution to the traditional diagnostic criteria requires more investigations. It is known that different diagnostic criteria are associated with different prognosis and a low grade of concordance among them can be observed in clinical practice (27,28). It is reasonable that different biomarkers, mirroring different aspects of pathophysiology of diabetes, could provide different information on the actual glucose homeostasis, explaining the different diagnostic accuracy. Moreover, although current guidelines recommended that elevated FPG, 2hPG, or HbA1c must be confirmed in a second blood sample for the diagnosis of diabetes (29), the validity for a confirmatory definition of undiagnosed diabetes based on a combination of two or more biomarkers measured on the single blood sample has been documented (28). In light of these considerations, the potential contribution of adding

different biomarkers to the common diagnostic workflow could be helpful to reach a better description of the real glucose homeostasis and, in turn, a better stratification of risk for patients that may have, or would develop, diabetes.

### Use of GA for monitoring hypoglycemic treatments and diabetes progression

Several clinical studies have evaluated the clinical use of GA in monitoring hypoglycemic treatments. The vast majority of these studies have been conducted on Asian populations with small sample sizes. Nevertheless, accumulating evidence supports the use of GA for early monitoring of treatment response in patients with diabetes (30-35). In a multicentre study, Lu *et al.* investigated the ability of GA to detect short-term changes of glycemic control in a group of more than 500 patients with newly diagnosed type 2 diabetes or needing a change in therapeutic regimen because of poor glycemic control, defined as having HbA1c >7% after at least two months of treatment. Patients on insulin treatment were excluded. In patients with improved glycemic control, GA declined to a greater extent than HbA1c at the early stages of treatment, indicating the higher sensitivity of GA than HbA1c for detecting short-term changes of glycemic control. Significantly, GA at day 14 was the strongest predictor of HbA1c variation at day 90, suggesting that GA after 2 weeks could detect the efficacy of therapy confirmed by HbA1c after a longer time (12). It has also been proposed that GA may serve for guiding diabetes treatment, for example for deciding to switch to a more intensive therapeutic regimen, or to discontinue hypoglycemic drugs basing on GA values (36). At present, the consequences in term of adverse outcomes of this approach have not been investigated yet. Taken together, these findings demonstrated that GA decreases faster than HbA1c in response to hypoglycemic treatment. This decrease can be observed just after 2–3 weeks from starting treatment. Moreover, the early measurement of GA can predict the change of HbA1c typically observed after 2–3 months. For these reasons, GA can be used as a biomarker of early treatment response. It could be speculated that GA may contribute effectively to short-term monitoring of hypoglycemic therapy reducing the time of exposure to an uncontrolled glycemia. It could be interesting to investigate the behaviour of GA in response to different drugs. To date, only few studies evaluated the response of GA to the therapy with different oral hypoglycemic drugs, or intensive treatments with insulin (11,31,37).

GA could be also considered an interesting biomarker to detect diabetes progression. Indeed, several studies have evaluated the ability of GA to predict future microvascular complications as well as cardiovascular events and mortality, in both patients with diabetes and in the general population (38-41). The association of GA with disease's progression and adverse outcomes could be explained with its propensity to non-enzymatic glycation and, in turn, its ability to serve as a biomarker of glycemic variability (42,43). A recent study evaluated the role of GA long-term variability as a predictor of the progression to diabetic nephropathy, finding that GA variability could be a significant predictor of the development of diabetic nephropathy, especially in patients with controlled diabetes (HbA1c <7.2%). These results could provide a pathophysiologic link between GA variability and disease's progression (44). Moreover, GA could reflect post-prandial glucose excursions in patients with type 2 diabetes treated with metformin, sulfonylurea and insulin, suggesting that GA could act as an alternative early indicator of disease progression (45).

### Use of GA in specific populations

The clinical use of GA has been investigated also in specific populations that may benefit from the introduction of alternative glycemic biomarkers.

The vast majority of paper published in the last years evaluating the clinical use of GA regards its measurement in patients with CKD, especially in the advanced stages. Indeed, GA has emerged as an useful marker of glycemic control in patients with CKD (46-49), particularly in those patients with altered hemoglobin turnover due to the use of erythropoietin stimulating agents, hemodialysis, frequent transfusion, or anemia, in which HbA1c typically underestimates the real glycemic homeostasis (50-53). The use of GA in this context has been evaluated also in relation to the main factors associated with altered albumin turnover. It is known that factors that interfere with albumin metabolism could affect GA levels, as it happens in patients with liver cirrhosis, hypo- or hyperthyroidism, obesity. It should be noticed that GA is commonly expressed as a percentage of total albumin, which is measured on the same sample at the time of GA measurement by the bromocresol purple method (54). This approach significantly reduces the influence of hypoalbuminemia on GA levels. Nevertheless, when albumin turnover is reduced or increased, its permanence in the bloodstream is altered, and, in turn, its glycation rate. Hypoalbuminemia

and albuminuria are very frequent in CKD patients, so the influence of such conditions should be evaluated carefully in this specific context. Okada *et al.* investigated the influence of proteinuria on GA levels in patients with diabetic CKD, finding that GA levels are not influenced by proteinuria, until it is in the nephrotic range (55). Recently, high GA levels have been associated also to a poor prognosis in patients with end stage renal disease, corroborating the use of the biomarker in this scenario (56,57).

Overall, the use of GA can be proposed when rapid changes in blood glucose occur, such as during pregnancy when HbA1c could overestimate the real glycemia due to iron deficiency. GA can be used also in monitoring gestational diabetes given the importance of maintaining under strict control hyperglycemic burden in this condition (58,59). Nevertheless, the use of GA for diagnosis of gestational diabetes is still controversial (60,61). Elevated GA levels, indeed, have been associated to adverse fetal outcomes (62,63). GA can be considered as an alternative biomarker of glycemia in those situations when HbA1c could lead to misleading results due to Hb variants, recent transfusions, anemia, use of erythropoiesis stimulating agents (64-68).

### Interpretative criteria for clinical use of GA

Generally, the definition of appropriate reference interval (RI) of a biomarker is mandatory to turn laboratory results into clinically valuable information. Indeed, before introducing a new biomarker in clinical practice, an in-depth knowledge of biological and pathological determinants that could interfere with its circulating levels, together with the distribution of the biomarker in healthy population, is required (69-71). Most of this information on GA is now available, facilitating its use in both research and clinical settings.

GA distribution was described in healthy subjects for the first time in the 1980s when the first studies describing its association with glycemic control were published (72-74). In these studies, however, inclusion criteria for patient selection and analytical methods for GA determination were very heterogeneous. The interest in GA increased much more in the 2000s when a new enzymatic method was developed in Japan, allowing the conduction of large clinical studies and the progress of the knowledge about its clinical use. Since the discovery, several methods for measuring GA levels have been proposed, including colorimetric assay (75), ion-exchange and boronate affinity chromatography (76,77); immunoassay (78); enzyme-linked boronate immunoassay

(ELBIA) (79), high-performance liquid chromatography (HPLC) (80); mass spectrometry (81) and enzymatic assay (82). Among these, the enzymatic method, which has been developed 15 years ago, is currently the most widely used allowing easy and rapid measurement of GA with good analytic performances. RIs of GA differ according to the method used for its measurement. While the first studies reported GA values of about 17.7–18.1% using a home-made method based on boronate affinity chromatography (9), most recent studies reported lower values using the enzymatic method. Ai *et al.* documented that in healthy controls selected on the basis of personal and family history and FPG <6.11 mmol/L, mean GA values were 13.2% and 13.5% in males and females, respectively (83). In a preliminary study that evaluated both analytical performance and clinical utility of GA, the authors found that GA median level was 13.4% in 32 blood donors included as control (84). Similarly, preliminary RIs have been reported by Testa *et al.* who documented that in a group of healthy subjects selected by FPG <5.55 mmol/L and/or HbA1c <39 mmol/mol, GA RI was 9–16% (85). Most of the present literature on GA, including that on RIs and on its distribution in healthy status, has been produced in Asiatic populations due to the widespread diffusion of the enzymatic assay in Asian countries. For example, Araki *et al.* studied more than three million blood donors in Japan and documented that mean GA ranged from 13.5%±1% to 13.8%±1.7% in subjects aged from 16 to 69 years, with a slight increase in females in comparison to males (86). With the specific aim of describing the RIs of GA, two large studies conducted in Italy and China reported comparable results (87,88). In the study of Bellia *et al.*, a large population of blood donors was included and the distribution of GA was described in relation to age and sex. The authors found that GA increased slightly at older ages, and confirmed that females have higher GA levels in comparison to males (87). The same association with age and sex was documented in the study by Zhou *et al.* The authors analysed a group of healthy subjects recruited during their routine healthy checks, reporting GA RIs separately for individuals aged 20–59 years as 13.38–13.89%, and for individuals aged 60–79 years as 10.23–14.79% (88). In a large community-based study, Selvin *et al.* reported that the GA RI was 10.7–15.1% (89). Again, GA was higher at older ages and in females than males. Also, the authors found a negative association between GA and BMI, with lower GA values in obese subjects. The association of GA with BMI has been largely documented in both diabetic and non-diabetic patients (17,25,90), and it has been linked



**Table 2** Reference intervals of glycated albumin evaluated by the enzymatic assay

Authors	Number of subjects	Study design	Ethnicity	Statistical approach	Reference limits
Paroni <i>et al.</i> (84)	32	Selected healthy subjects	Caucasian	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	11.7–16.9%
Testa <i>et al.</i> (85)	252	Selected healthy subjects	Caucasian	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	9–16%
Bellia <i>et al.</i> (87)	1,334	Blood donors	Caucasian	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	<14.5%
Zhou <i>et al.</i> (88)	458	Selected healthy subjects	Asian	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	10.38–13.89% (20–59 years); 10.23–14.79% (60–79 years)
Selvin <i>et al.</i> (89)	1,799	Community-based	Caucasian, African American	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	10.7–15.1%
Matsha <i>et al.</i> (93)	663	Selected healthy subjects	Mixed (Black African, Caucasian, mixed-ancestry)	Non-parametric, 2.5 <sup>th</sup> –97.5 <sup>th</sup> percentile	10.7–15.2%
Hiramatsu <i>et al.</i> (94)	676	Selected healthy pregnant	Asian	Parametric, mean $\pm$ 2SD	11.5–15.7%

DS, standard deviation.

to the faster catabolism of albumin due to a higher grade of subclinical inflammation in obesity (91). In a recent study by Wang *et al.*, a total of 86,319 clinical lab results were analysed in order to evaluate the influence of several pathological conditions on GA levels. The mean value of GA in healthy controls was 11.7% (92). Interestingly, Authors found that GA is increased in patients with diabetes, as expected, but also in patients with coronary artery disease, uremia, cerebrovascular disease, diabetic nephropathy, cirrhosis and several cancers. On the opposite, GA is lower than controls in nephrotic syndrome, preeclampsia, leukemia, lupus erythematosus, sepsis. Nevertheless, the study lacks of a detailed description on how “healthy” status was defined. The distribution of GA has been described also in healthy Black Africans, with slightly higher values in comparison to Caucasian and mixed-ancestry (93). Finally, Hiramatsu *et al.* studied a group of 676 healthy pregnant women and follow-up them monthly during pregnancy and after delivery (94). The authors reported that the RI for pregnant women was 11.5–15.7%, and that GA values trended to decrease during pregnancy, especially in the third trimester. *Table 2* reports the main studies describing the RIs of GA in healthy populations obtained by the enzymatic assay. Noteworthy, when comparing GA values, it should be considered that a significant variability among different analytical methods exists.

## Conclusions and future perspectives

GA is the result of a non-enzymatic process that leads to the formation of a stable product arising from the condensation of plasma glucose and circulating albumin. Due to the shorter half-life of albumin in comparison to haemoglobin, GA is considered a medium-term biomarker of glycemic burden, providing information about glycemic status during the 3–4 weeks before blood sampling. For these reasons, GA has been proposed for early monitoring of hypoglycemic treatments in patients with both type 2 and type 1 diabetes. Moreover, GA has been proposed as an additional biomarker for diabetes diagnosis, especially when traditional diagnostic criteria are inconsistent. The introduction of GA in clinical practice is facilitated by the knowledge of its distribution in healthy subjects and in the general population, together with its biological variation, allowing the appropriate interpretation of results. Nevertheless, despite this encouraging evidence, many aspects of GA clinical use have to be further investigated. For example, the long-term efficacy of a biomarker-oriented management of therapy based on GA values hasn't been described yet. Finally, the use of GA in relation to the current biomarkers of hyperglycemia requires further investigations. A rational approach to the introduction of GA in clinical practice is to consider GA not as an alternative, but as a complementary biomarker to traditional glycemic metrics, such as HbA1c,

reflecting different aspects of glucose homeostasis.

In conclusion, the introduction of new biomarkers of glycemic control is advocated for a more accurate description of the real glucose burden into circulation in diagnosis and diabetes treatment. GA has emerged as a promising biomarker of glycemic status that could overcome some of the limitations of the traditional metrics.

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