

## Review Article

# Glycated albumin as medium-term glycemic control in diabetes mellitus

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## ABSTRACT

Monitoring of glucose levels is essential in preventing the complications of diabetes mellitus, including short, medium and long-term monitoring. Short-term monitoring includes random plasma glucose, fasting plasma glucose, 2-hour post prandial plasma glucose and Oral glucose tolerance tests (OGTT). The medium-term monitoring includes fructosamine and Glycated albumin (GA) while the long-term monitoring is glycated hemoglobin (HbA1c). Currently, the most recommended examination for glucose level monitoring in patients with diabetes mellitus is the glycated hemoglobin (HbA1c). However, there seem to be some conditions where the HbA1c value is doubtful or unreliable. Some of these conditions include anemia, thalassemia, dialysis and pregnancy. The best choice at this time is GA.

**Keywords:** Diabetes mellitus, Glycated albumin, Glycemic status

## INTRODUCTION

Diabetes mellitus (DM) is a systemic disease produced by an increase in blood glucose levels as a result of a gradual decrease in insulin secretion.<sup>1</sup> Persistent hyperglycemia in diabetes is frequently connected with abnormalities and malfunctions in numerous organs of the body, including the kidneys, eyes, heart, nerves, and blood vessels.<sup>2,3</sup> DM can lead to long-term consequences, such as diabetic ulcers (15%), which result in amputation in 85 percent of cases.<sup>4</sup> Plasma glucose levels, HbA1c, and Glycated albumin (GA) values are used to diagnose diabetes.<sup>5-7</sup>

GA is the result of non-enzymatic oxidation processes that produce a link between albumin and glucose molecules. GA, like fructosamine, is a glycemic control index that is unaffected by hemoglobin metabolism issues. Furthermore, GA indicates a shorter glucose status than HbA1c, which reflects values from 2-4 weeks ago. Because GA determines the ratio between glycated

albumin levels and total serum albumin, it is unaffected by changes in blood protein levels like fructosamine.<sup>8,9</sup>

Glycation is a process in which sugar molecules, such as glucose or fructose, link with protein or lipid macromolecules without the use of enzyme catalysts.<sup>10</sup> Glycation of all types of proteins, including albumin, causes an increase in plasma glucose levels in diabetics.<sup>11</sup> Non-enzymatic glycation of serum albumin produces GA, a ketoamine.<sup>8,12</sup>

Changes in erythrocyte age have no effect on the value of GA and anemia or other factors that invalidate the measurement of HbA1c in the diagnosis of diabetes have no effect on GA measurement.<sup>12,13</sup>

Several studies have shown that GA is more reliable in monitoring DM and a better marker in glycemic control compared to HbA1c in hemodialysis patients and patients with fluctuating glucose levels or DM with poor control.

Factors interfering with hemoglobin metabolism have little effect on serum GA levels.<sup>14</sup>

### **Glycated albumin (GA)**

#### *Metabolism of albumin*

In the human body, albumin is synthesized by the liver about 100-200 µg/g of liver tissue each day. Furthermore, albumin is distributed vascularly in plasma and extravascularly in skin, muscle and several other tissues. Albumin synthesis in liver cells happens in two places. The first is on the free polysome where albumin is formed for intravascular purposes. The second is on polyribosomes binding to the endoplasmic reticulum where albumin is produced for systemic distribution.<sup>15</sup>

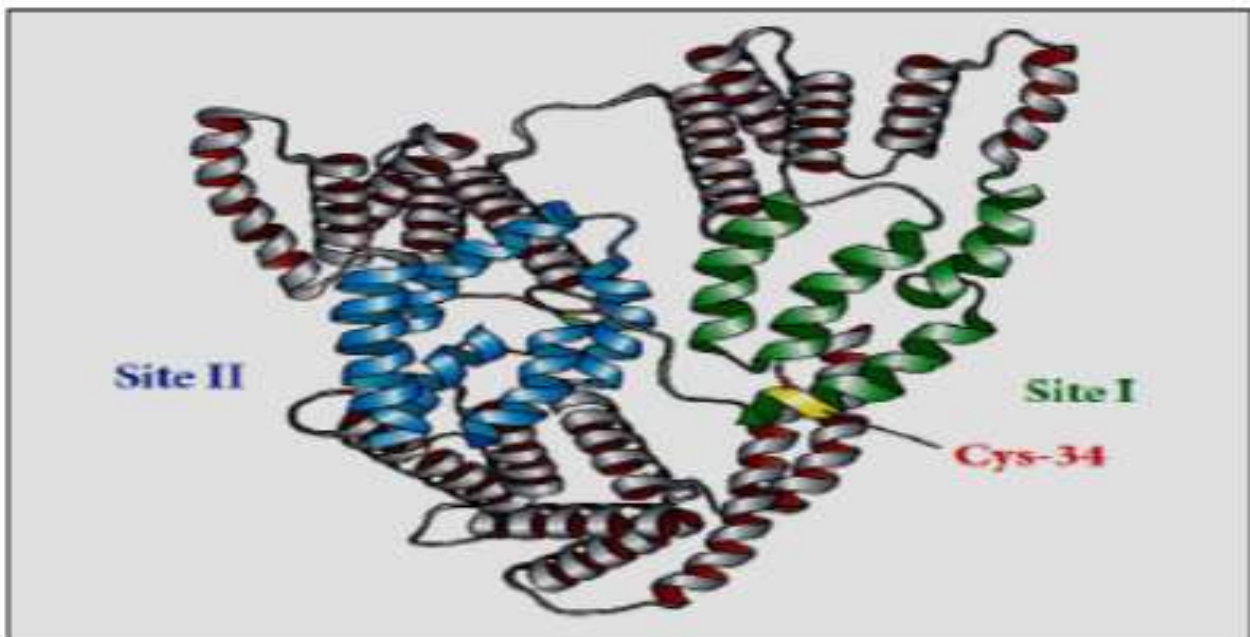
Albumin synthesis can be influenced by several factors, namely nutrition specifically amino acids, hormones and the presence of a disease. Amino acids which can stimulate albumin synthesis are tryptophan, arginine, ornithine, lysine, phenylalanine, threonine and proline, while the hormones which can induce albumin synthesis are thyroid hormone, growth hormone, insulin, adrenocorticotropin, testosterone, and the hormones produced in adrenal cortex. On the other side, alcohol can inhibit albumin synthesis. Secondly, diseases which can cause disorders of albumin synthesis are chronic liver disease, kidney failure and nutritional deficiency such as Kwashiorkor.<sup>15</sup>

#### *Process of albumin glycation*

Albumin is one of the longest known and the largest component of plasma proteins, representing more than 80% of total molecules and 60% of total plasma protein concentrations making it the most abundant plasma protein

with various physiological functions.<sup>16,17</sup> Structurally, albumin is made up of 585 amino acids and contains 35 essential cysteine residues (except Cys-34) which form disulfide bridges building the tertiary protein structure as a whole (Figure 1).<sup>15</sup>

Glycation (also known non-enzymatic glycosylation) is a very simple process in which excessive sugar molecules such as fructose or glucose attach themselves to normal protein or lipid molecules in the blood without any enzymatic intervention (Figure 2).<sup>15</sup> Monosaccharides have various innate glycation activities; it is known that galactose and fructose have about 10-times-greater glycation activity than glucose. The concern about glycation in diabetes arises from the fact that reduced sugars have the potential to induce glycation and impair the function of a number of proteins. Since all proteins are susceptible to glycation, the disruption can have significant effects. Glycation products can be classified into early products and advanced products. Initially, a reversible and unstable Schiff base is formed by bonding of glucose or its derivatives with albumin with a free amino (reversible glycation, 1-2 weeks glycation), leading to the formation of stable fructosamine residues (ketoamines) through removal of water. Rearrangement of these compounds eventually result in irreversible Amadori compounds (irreversible glycation, 6-8 weeks glycation). This is defined as the initial glycation process and is also known as the Maillard reaction. Advanced modifications to these early glycation products (Amadori adduction), such as rearrangement, oxidation, polymerization, and division, create irreversible conjugates called Advanced glycated end products (AGEs). AGE products are considered as markers in various diseases such as arteriosclerosis, kidney failure, Alzheimer's disease, or diabetes, and also increase during the aging process.<sup>8,15,18</sup>



**Figure 1: Structure of albumin.**<sup>15</sup>

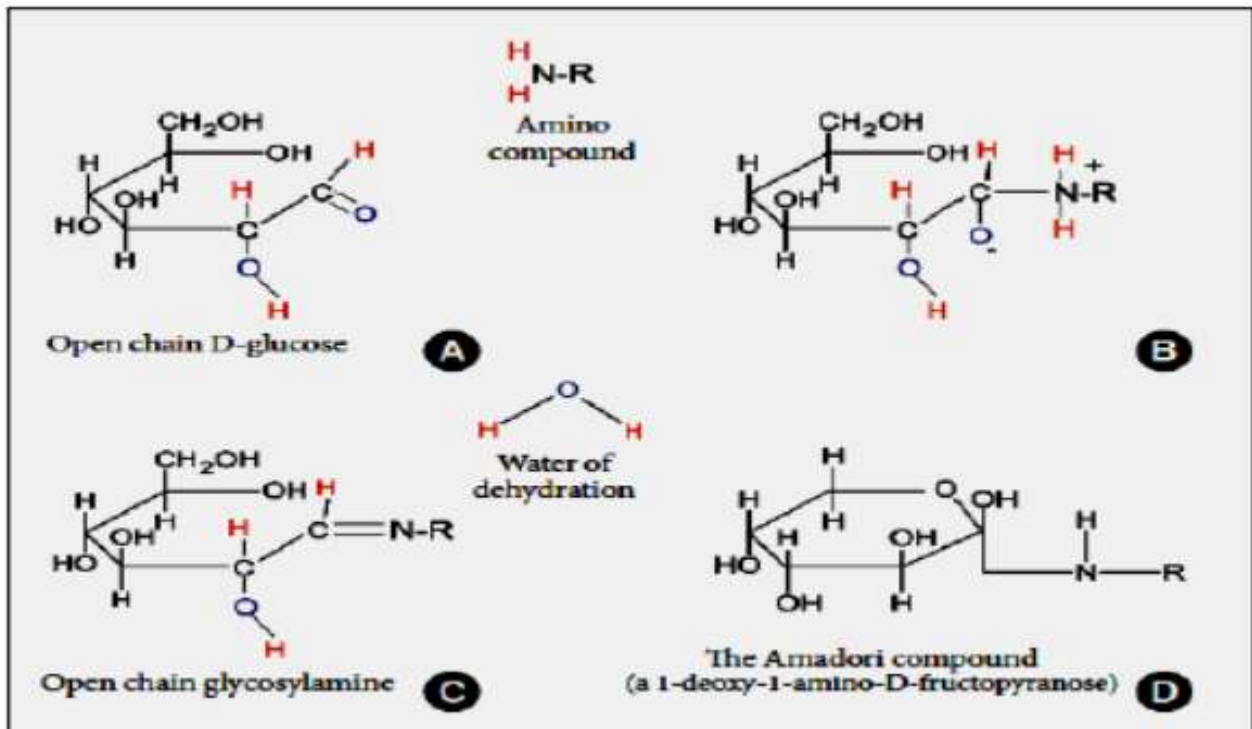


Figure 2: The process of albumin glycation.<sup>15</sup>

### Benefits of GA

Faster monitoring of changes in plasma glucose levels

The half-life of serum albumin is shorter than erythrocytes. This compromises that GA levels alter more quickly when there is a change in glucose control status within a short time. Short changes usually occur because of external therapeutic factors, such as oral medication or insulin injection.

On the other hand, GA levels are also better than HbA1c when blood glucose status deteriorates (an increase in glucose levels) in a short period. In this case, GA catches the signal for an earlier rise in glucose levels compared to HbA1c. HbA1c remains normal or shows a slight increase in the diagnosis of fulminant type 1 Diabetes mellitus (DMT1), where pancreatic  $\beta$  cells are destroyed rapidly, resulting in increased plasma glucose levels and a very brief ketoacidosis. In these cases, GA is a better parameter than HbA1c because it quickly depicts changes in plasma glucose status induced by treatment effects.<sup>8</sup>

Changes of glycemic status in GA, which are quicker than HbA1c, can help clinicians in giving the optimal dose to patients who are on medication. With a faster response to changes in plasma glucose levels, GA is valuable for adjustment of therapeutic dose for patients on therapy. Takahashi et al., found a significant decrease in GA levels compared to HbA1c levels with intensive insulin therapy, although in the end the percentage of the decline in HbA1c and GA would be similar at 16 weeks of therapy. The GA/HbA1c ratio markedly decreased at 8 weeks of

therapy, and gradually increased over the following 8 weeks. Thus, GA can be used as a more sensitive monitoring parameter to detect improvements in glycemic control in the early period of therapy. This explains that GA can describe treatment effects much better, so that clinicians can provide dose adjustments to patients more.<sup>8,9</sup>

Monitoring of plasma glucose levels in patients on dialysis and patients with anemia

It is known that in patients with end-stage renal damage requiring hemodialysis, the lifespan of erythrocytes is shortened. This causes a decrease in HbA1c levels (falsely low) which makes the examination of plasma glucose levels using HbA1c unreliable.

During hemodialysis, uremia, blood loss on treatment, and frequent blood draws can all contribute to a reduction in the half-life of red blood cells. Shortened erythrocyte half-life and transfusion can decrease HbA1c levels, potentially rendering glycemic control assessments un dependable. Studies have shown that HbA1c levels are relatively lower in patients with diabetes mellitus on dialysis compared to then GA levels. In patients with end-stage CKD or ESRD, low HbA1c levels are correlated with low hemoglobin levels and high therapeutic doses of erythropoietin.<sup>19</sup> Erythropoietin is a hormone which promotes erythrocyte formation and increases erythrocyte survival. However, patients on dialysis with low hemoglobin levels may have reduced erythrocyte survival and decreased hemoglobin half-life, which cannot be cured with high doses of erythropoietin. This shows that GA can be a better parameter than HbA1c in hemodialysis patients.<sup>19</sup>

### Monitoring of blood glucose levels in pregnancy

Glycemic control in pregnant women with diabetes or gestational diabetes is necessary to reduce the risk of fetal death and maternal complications. Studies showed a decrease in HbA1c levels in the second trimester, followed by a significant increase in the third trimester of pregnancy. From the second trimester to the third trimester of pregnancy, HbA1c levels increased, saturated transferrin declined, and ferritin levels decreased, while GA levels did not show significant changes.<sup>20,21</sup>

Changes in HbA1c levels during pregnancy are assumed to be caused by iron deficiency. This happens because most pregnant women experience iron deficiency. Transferrin and ferritin levels were found to be relatively lower in pregnant women. Ferritin is the most important iron storage protein in the body, while transferrin is a protein that carries iron in the blood. HbA1c levels were found to have a negative correlation with saturated transferrin and ferritin. The increase of HbA1c in late pregnancy is strongly influenced by iron deficiency.<sup>20,21</sup>

The inverse correlation between HbA1c and iron concluded that the increase in HbA1c was the result of iron deficiency in the third trimester of pregnancy, both in healthy women and in women with diabetes mellitus. This shows that HbA1c is not a good control index for monitoring plasma glucose levels in pregnancy. In this case, since GA is not affected by iron deficiency and can reflect short-term changes in blood glucose mean, GA can be a better parameter for monitoring glucose levels.<sup>20,21</sup>

### Monitoring of postprandial hyperglycemia and glucose fluctuation

Several epidemiological studies have shown that postprandial hyperglycemia is a risk factor for cardiovascular disease. A study by Funugata demonstrated that the postprandial plasma glucose in glucose tolerance test was a stronger risk factor for cardiovascular events than the fasting plasma glucose. In addition, it was reported that administration of the  $\alpha$ -glucosidase inhibitor acarbose to patients with impaired glucose tolerance or diabetes mellitus was associated with reduced cardiovascular risk.<sup>22</sup>

Furthermore, GA can capture changes in postprandial glucose levels compared to mean plasma glucose and HbA1c. The GA/HbA1c ratio in DMT1 patients which is greater than in DMT2 shows that GA better describes these fluctuations, since in general, DMT1 patients have higher glucose fluctuations than DMT2. Based on this phenomenon, in DMT1 and DMT2 patients who showed no difference in HbA1c levels, GA levels were significantly higher. This suggests that GA may reflect postprandial plasma glucose levels and various fluctuations in plasma glucose better than HbA1c.<sup>23</sup> The DCCT study showed that intensive insulin injection could lower the risk of retinopathy compared to conventional

insulin in DMT1 patients, even in the absence of changes of HbA1c levels. Intensive insulin injection was thought to reduce fluctuations and changes in blood glucose levels, hence will diminish the risk of microangiopathy. Postprandial glucose levels were found to be a better predictor of diabetic retinopathy than HbA1c in DMT2. Increased glycemic fluctuations and/or postprandial glucose changes have been associated with a higher risk of diabetic macroangiopathy. GA as a short- to medium-term parameter can describe changes/fluctuations in plasma glucose. Yoshiuchi et al explained that the GA/HbA1C ratio was higher in DMT1 patients than DMT2 patients, where there was a fairly high fluctuation of blood glucose levels in DMT1 patients.<sup>23,24</sup> The DCCT (Diabetes control and complication trial) showed that independently, GA and HbA1c were excellent parameters for microangiopathy risk. The strongest correlation was when GA and HbA1c levels were combined as parameters, thus complementing each other from the potential of each measurement as a risk factor.<sup>25</sup>

GA as an alternative marker of glycemic status in patients with fructosamine, GA and HbA1c, are non-enzymatic glycosylated proteins used as markers of glycemic control in diabetic patients. GA is a form of bond between albumin and glucose molecules through non-enzymatic oxidation reactions. Similar to fructosamine, GA is an index of glycemic control which is not affected by disorders of the hemoglobin metabolism. In addition, GA reflects a shorter glucose status compared to HbA1c which reflects the levels of 2-4 weeks earlier. Glycosylated albumin is not impacted by changes in serum protein levels like fructosamine, since GA calculates the ratio between the glycosylated albumin levels and total serum albumin.<sup>8</sup> Glucose binds strongly to serum albumin at the 4 lysine residue sites, and the glycation reaction occurs 10 times faster than the glycation of hemoglobin. Therefore, GA can better capture fluctuations and changes in glycemic status more quickly and significantly than HbA1c.<sup>24</sup>

GA describes glycemic control in a brief period of time, but GA is not impacted by serum albumin levels because it is calculated from the ratio of total serum albumin. Several studies have reported the reference value of GA. Among others, in a study by Tominaga et al in the Japanese population the value was 12.3-16.9%.<sup>22</sup>

A study by Kohzuma et al obtained the reference value of GA in the American population as 11.9-15.8%.<sup>26</sup> According to a research by Roohk et al, the target of glycemic control as measured by GA parameters was <20%, with a normal value of 11-16%.<sup>16</sup> A study by Pu et al about the predictive values of GA and HbA1C in assessing coronary heart disease in patients with DMT2 using Receiver operating characteristic (ROC) curve showed that GA was 0.620 (62%) better than HbA1C (54.3%), with a GA cut off point of 19%.<sup>27</sup> Within the last 15-20 years, apart from GA, there have been abundant published reports describing the assay of serum protein markers such as Fructosamine (FA) as a method for



assessing glycemic status in an intermediate period (2-4 weeks). It is named fructosamine because of its similar chemical structure to fructose which refers to the sum of all the ketoamine bonds resulting from glycation of circulating serum proteins. A rapid test for FA was described by the FDA in 1997, and several clinical studies have been reported with varying results, but the winding commercial pathways for this test have made it difficult to provide, hence it is no longer available as a rapid commercial test.<sup>16,28</sup>

### Conditions which affect GA results

#### Liver cirrhosis

The liver is a vital organ which is important for regulation of plasma glucose levels. Glucose metabolic disorders occur frequently in patients with chronic liver disease, such as chronic hepatitis and liver cirrhosis. In patients with chronic liver disease, about 70-90% are diagnosed with impaired glucose tolerance and 30-60% of them are diagnosed for DM.

It is very important to keep the blood glucose levels under control in these patients. HbA1c has a low correlation in patients with chronic liver disease, due to a shortened erythrocyte lifespan. On the other hand, the values of GA and fructosamine were higher in these patients, possibly caused by the prolonged half-life of serum albumin due to decreased albumin synthesis. It is very difficult to monitor blood glucose levels in patients with chronic liver disease because currently there are no parameters that work well in this condition.<sup>8</sup>

#### Disorders of the albumin metabolism

GA shows lower values in patients with nephrotic syndrome, hyperthyroidism and steroid treatment such as glucocorticoids which may increase albumin metabolism. The declining GA levels in these conditions is caused by the shortened half-life of serum albumin due to increased metabolism of serum albumin. Contrarily, GA shows a higher value than plasma glucose levels in patients with liver cirrhosis and hypothyroidism where albumin metabolism diminishes.<sup>8</sup>

### CONCLUSION

GA can be a better biomarker of glycemic control compared to HbA1c, specifically the changes of glycemic status in diabetes mellitus type 1 and 2. GA reflects a shorter blood glucose status than HbA1c, which is within 2-4 weeks earlier. Glycated albumin is affected by liver cirrhosis and albumin metabolism disorders such as nephrotic syndrome, hyperthyroidism and steroid treatment.

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