Glycated Albumin: A Better Biomarker for Short-term Glycemic Control

Introduction

Plasma and intracellular proteins can undergo non-enzymatically controlled glycation with the attachment of carbohydrate moieties to exposed amino acids within the structure of the protein molecule. The degree of glycation is dependent upon the concentration of carbohydrate within the plasma or intracellular matrix. Most notable is hemoglobin A1c (HbA1c) within the red blood cell (RBC), that constitutes a diabetic marker used in diagnosis and monitoring glycemic disorders. The methods for measuring HbA1c specifically target the glycation of glucose attached to hemoglobin. Since RBCs have a half-life of 90-120 days, HbA1c provides a mechanism to assess the average blood glucose level over the preceding 2 to 3 months.[1] This fact limits the clinical sensitivity of HbA1c in those medical conditions where glucose homeostasis is dynamic, the erythrocytic life span or hemoglobin metabolism are not stable, or the clinical condition mandates more immediate glycemic assessment.[1]

All plasma proteins are known to undergo glycation, whereby albumin constitutes 60-70% of the blood total proteins.1,2 Since the half-life of albumin is 2-3 weeks,[2] the measurement of glycated albumin (GA) provides a means to assess short-term glycemic control in those conditions where HbA1c utility is limited.

Gestational Diabetes Mellitus

Strict glycemic control is imperative in women with gestational diabetes to limit adverse perinatal complications, such as macrosomia.[5] In gestational diabetes mellitus (GDM), HbA1c may not accurately reflect glucose homeostasis in certain conditions such as iron deficiency anemia, hemolytic anemia, uremia, and hemoglobinopathies.[5] In addition, HbA1c rises during pregnancy, peaking in the third trimester due primarily to hemodilution.[6] Alternatively, GA is not affected by hemoglobin metabolism, anemias, nor by pregnancy, and may be a more suitable method of assessment.[2,5] GA was also correlated with fasting and postprandial glucose regardless of insulin resistance and blood pressure in women with GDM.[7]

Glycated Albumin vs Fructosamine vs HbA1c

Fructosamine (FA) is a measure of total serum glycated proteins. As a result, this measurement is not without limitations, especially since the analysis is not widely standardized.[1] Since the measurement of FA involves a chemical dye reduction, reducing agents like vitamins and bilirubin at higher concentrations can bias the test results, which do not influence the enzymatic method for GA.[1] FA results can also be influenced by pathological fluctuations in blood protein levels resulting in hypoproteinemic states such as protein losing gastroenteropathies, nephrotic syndrome, hepatic cirrhosis, and thyroid disease.[1,8] GA is not affected by these conditions since it is reported as a percentage ratio of serum glycated albumin to total serum albumin.[6] FA is also influenced by high concentrations of immunoglobulins, especially IgA.[1] In patients with chronic kidney disease (CKD) and undergoing renal dialysis or peridialysis, GA is now considered a superior index of glycemic control, whereby dialysis can have a significate impact on HbA1c, but not GA.[1,9] It is also interesting to note that GA was not influenced by the glomerular filtration rate, but HbA1c was.[1] FA also is correlated to gestational age in pregnancy, thus complicating the assessment of glycemic control at various stages of gestation in GDM.[1]

Clinical Usefulness

As mentioned, HbA1c has limitations in which glycemic control may not be accurately reflected. In these conditions, GA measurement may be a more appropriate. This list reflects literature reports in which the use of GA has been preferred over HbA1c.[3,4]

- At rapid improvement or aggravation of glycemic control status
- At onset of fulminant Type 1 diabetes mellitus
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus under insulin therapy
- Patients with marked postprandial hyperglycemia (eg, gastrectomy)
- Patients treated with drugs targeting postprandial hyperglycemia
- Hemolytic anemia, hemorrhage, blood transfusion
- Variant hemoglobin
- Chronic renal failure (especially those patients undergoing dialysis)
- Liver cirrhosis
- Iron deficiency anemia, iron deficiency status
- Treatment phase of iron deficiency anemia
- Pregnancy
- G6PD variants causing unstable red blood cells

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Reference Intervals

Selvin, in an analysis of 11,737 individuals from the ARIC (Atherosclerosis Risk in Communities) study comprised of white and black individuals in the U.S., determined that the GA cut points were 13.6% to 15.6% percentile equivalents to HbA1c[11]:

- Range — 10.7% to 13.5%;
- Prediabetes — 13.6% to 15.5%;
- Diabetes — >15.5%.

Factors Influencing Levels of HbA1c[10]

Process	Factors	Effect on HbA1c level
Erythropoiesis	Iron/vitamin B12 deficiency, decreased erythropoiesis	Increased
	Erythropoietin administration, iron/vitamin B12 deficiency, reticulocytosis, chronic liver disease	Decreased
Hemoglobin modification	Genetic or chemical modifications of hemoglobin (hemoglobinopathies, HbF, methemoglobin)	Increased or decreased
Glycation	Alcoholism, chronic renal failure, decreased erythrocyte pH	Increased
	Aspirin, vitamin C and E,, certain hemoglobinopathies, increased intra-erythrocyte pH	Decreased
	Genetic determinants	Increased or decreased
Erythrocyte destruction	Increased erythrocyte life span (eg, due to splenectomy)	Increased
	Decreased erythrocyte life span (eg, due to hemoglobinopathies, splenectomy, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone)	Decreased
Analytical interferences	Hyperbilirubinemia, carbamylated hemoglobin, alcoholism, high-dose aspirin, chronic aspirin opiate use	Increased
	Hemoglobinopathies	Increased or decreased
	Hypertriglyceridemia	Decreased

Relevant Assays*

Test Name	Test Number
Glycated Albumin	123030

*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.Labcorp.com.

References

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