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REVIEW ARTICLE

# Potential Benefits and Concerns with Measuring 1, 5-Anhydroglucitol as a Marker of Glycemia

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**Abstract:** ***Levels of 1, 5-anhydroglucitol (1,5-AG) have long been postulated to be a measure of post-meal glucose excursion and 1,5-AG existsin a large pool in our body. In case of glucosuria due to hyperglycemia the renal tubular reabsorption of 1,5-AG is inhibited and its concentration in the serum decreases. The level of 1, 5-anhydroglucitol can be an alternative to HbA1c, which is a standard index for glycemic control, and for monitoring the pattern of glycemic excursions in patients with well-controlled and moderately controlled type 2 diabetes. The 1, 5-AG assay reflects glycemic excursions in the postprandial state more precisely than some other methods available for the same. A test for measuring 1, 5-AG has received US FDA approval for monitoring short-term glycemic control as early as in 2003. This article refers to the source of 1, 5-AG, its structural similarity to glucose, its measurement, its role in improving patient care and future aspects as well as concerns.***

## Introduction

The limitations of measuring single random blood glucose samples are well known. The HbA1c and serum fructosamine assay are well established methods to ascertain glycemic control of individuals over the past 2-3 months and 3-4 weeks respectively. Continuous Glucose Monitoring System (CGMS) and Self-Monitoring of Blood Glucose (SMBG) can also be used to monitor daily blood glucose. But some of these methods need multiple samplings which is very difficult in practical world. Multiple sampling can be painful whether it is a finger stick testing or blood collection. In addition, testing repeatedly at home is cumbersome, painful and patient often forget to test in addition to increasing anxiety.

Though the HbA1c test requires only one sample (and does not require fasting), its result is mostly influenced by postprandial blood glucose (PPBG) level. But it is difficult to precisely estimate the exact contribution of PPBG to the HbA1c. HbA1c result can be affected by various types of anemia, hemoglobinopathies, hemolysis, certain drugs, uremia and splenomegaly. Result of serum fructosamine assay can be affected by defective albumin, thyroid diseases, liver disease and hypertriglyceridemia.

Hence there is a need for a marker which can give an estimate of PPBG over several days with one blood sample and which is least affected by other confounding factors.

The 1, 5-Anhydroglucitol (1,5–AG) test, also called Glyco Mark is approved in USA for use as a glycemic

marker indicating glycemic level of post prandial blood glucose over the past 4-5 days with single test. Sample can be taken at any time, irrespective of previous food intake.

The main source of 1,5-AG is from the diet, but dietary variation of this compound was not shown to affect its results when used as a marker. Actually, 1,5-AG is absorbed through the intestine and distributed to all organs and tissues via the blood. Serum 1, 5-AG level is inversely proportional to blood glucose level. During high blood glucose levels there is a reduction of 1,5-AG reabsorption in the renal tubule and hence it is excreted in urine thereby leading to a low serum level of 1,5AG. Thus, high glucose level lowers 1,5-AG level and low glucose level raises 1,5-AG level.

## What is 1, 5- Anhydroglucitol?

Structurally,1,5-anhydroglucitol (1,5- AG) is a six-carbon monosaccharide, with a half-life of ~ 1 to 3 days. [1,4,7]This was discovered in the plant family *Polygala Senega* (1888).It is a non-metabolizable glucose analogue and its daily dietary intake equals its urinary excretion there by maintaining constant blood glucose levels.[2]In studies, 1, 5-AG has been found to be a short- termmarker of glycemic control in diabetes as it responds within 24h due to glucose's competitive inhibition of 1,5- AG reabsorption in the kidney tubule.[1] To put it simply, in the steady state, the nutritional intake contributes to 1,5- AG, but the loss of 1,5-AG in the urine leads to a constant blood level.

As mentioned earlier 1, 5-AG is a monosaccharide, a 1-deoxy form of glucose. Glycemic biomarkers such as fructosamine, glycated albumin (HbA1c) and 1,5- AG are important tools for determining the metabolic control and glycemic variability of a diabetic patient. There is a close association of 1,5-AG with glucose fluctuations as well as postprandial glucose and therefore, gives more accurate medium term assessments of repeated and rapid glycemic changes than either fructosamine or HbA1c.[5,9]

## How 1,5-AG is Excreted in Urine?

Actually, 1,5-AG is filtered by the glomerulus. However, its reabsorption depends on the prevailing glucose levels in the blood and urine. When blood glucose is high (hyperglycemia), more glucose is filtered. Thus, this filtered glucose that reaches the renal tubules now begins to compete with 1,5-AG, with the result that more glucose is reabsorbed and thus more 1,5-AG is excreted. As both 1,5-AG and post-prandial hyperglycemia are related to nutritional intake, 1,5-AG is more of an index of post-meal glucose levels.

## Methods Available for Measuring 1,5-AG and Post-Prandial Blood Glucose

During the hyperglycemic state in response to the high blood glucose levels the reabsorption of 1,5-AG is inhibited and hence as the glucose level increases in the blood, the 1,5- AG level goes down. 1,5-AG level reflects past day to a week's glucose level as compared to HbA1c (past 2-3 months average) and fructosamine (past 2-3 weeks average). 1,5- AG can be measured colorimetrically with enzymatic biochemical analysis,[3]by electrochemical impedance spectroscopy (EIS),[12] LC-MS/MS (Liquid chromatography-mass spectroscopy). The GlycoMark test is approved by US Food and Drug Administration (FDA) for monitoring glucose control for people with diabetes and also certified for the same use in Europe.

## GlycoMark™ and its Accuracy

GlycoMark is a test for measuring 1,5- AG level which gives an idea of the maximum average blood glucose level for the past two weeks.[1,3] This is beneficial for the patient and the physician to keep a check on whether the blood glucose levels are relatively stable or getting worse. This can even detect glycemic fluxes when HbA1c is static and when there are consistent post-prandial glucose surges. The 1,5-AG level testing is applicable to both serum

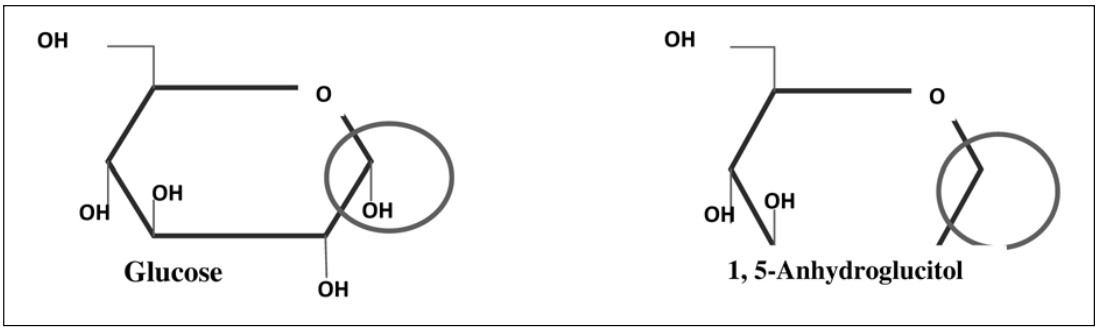


**Figure 1.** The unique structural similarity of 1,5-AG to glucose

and plasma estimations. The test is a two-step enzyamtic method. The serum or plasma sample is first pre-treated with glucokinase, converting glucose to glucose-6-phosphate thereby altering glucose which is also present in the blood sample so that it dose not react in the next step of the reaction. Then pyranose oxidase oxidizes the second hydroxyl group of 1,5- AG to generate hydrogen peroxide. The amount of the product, hydrogen peroxide acted upon by peroxidase, is estimated colorimetrically and it is directly proportional to 1,5- AG concentration in the serum.[14]

## What are the Cut-off levels for Detecting Abnormal Glucose Concentrations?

Measuring 1,5-AG can be correlated with either HbA1c or mean PPBG levels (see table no. 1&2). Less than 10mg/ml 1,5-AG values are an indication of hyperglycemic excursions above 180mg/dL for the past 1-2weeks. It is well known that a level of 180mg/dL is the renal threshold value for people with normal blood glucose levels. The general normal 1,5-AG levels ranges from 11-24µg/ml. A measurment of 10µg/ml of 1,5-AG correlates to an average PPBG (post-prandial blood glucose) of 185mg/dL. Hence, if the physician wishes to keep the mean PPBG level to below 185mg/dL, the desirable value of 1,5-AG would be 10µg/ml or more. The 1,5-AG test is not affected by Hb, triglycerides, bilirubin, glucose (1000mg/dL), uric acid/urea (20mg/dL) and creatinine (10mg/dL). Certain factors like advanced stage of kidney disease (stage 4-5), liver disease, pregancy, drugs like acarbose, use of diabetes agents like SGL2 inhibitors (sodium-glucose transporter-2), use of steroids and certain chinese medicines like polygala, tenuifolia may cause spuriously high 1,5-AG levels.

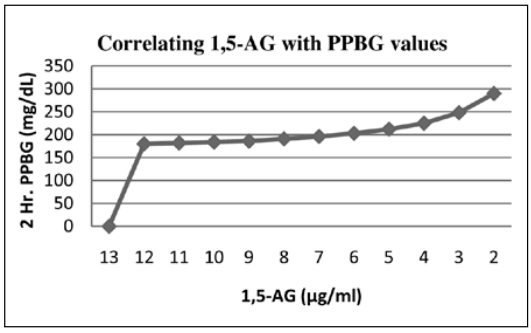


**Figure 2.** Correlating 1,5-AG with PPBG values. The lower the 1,5-AG value, the higher the mean daily peak glucose. Because 1,5-AG is getting excreated in urine, which lowers 1,5-AG's serum level in the blood.[21]

## Can 1,5-AG Improve Patient Care?

As shown in figure 2. 1,5-AG level (<2µg/ml) is associated with very high postprandial glucose levels (>290mg/dL) well as high HbA1c (>10%). Research has been conducted around the world comparing Glycomark with other glucose monitoring tests , oral glucose tolerance tests, HbA1c and fructosamine. It has been studied for Type 1, Type 2 and gestational diabetes. Hemoglobinopathies does not interfere with this test as this is not a hemoglobin glycosylation marker like HbA1c.The standard dignostic test HbA1c dose not accurately differntiate between fasting blood glucose level and postprandial blood glucose level.For example, approximately only two-thirds of the contribution of HbA1c is from the post-prandial and post-absorptive gluose levels. On the other hand,1,5- AG has the ability to reflect glycemic variability and postprandial hyperglycemia scrupulously.[6,8,10]It has been reported that low concentrations of 1,5- AG are srtongly associated with prevalent retinopathy and incident chronic kidney disease.[11]An added advantage is the patient does not need to come in the fasting state for diagnosis. Thus,1,5- AG could be an valuable alternative to self-monitoring of blood glucose in diabetic patients with normal or near normal glycemic control.1,5-AG is of note more applicable to patients with moderately controlled diabetes whose HbA1c d"8.0% as it depends on the renal tubular reabsorption of glucose. Glycemic markers like glycated hemoglobin (HbA1c), fructosamine and self- monitoring of blood glucose allows measurment of glucose in fasting, timed or randomly which gives you the mean average of glycemic exposure. But, assessment of glycemic variabilities are increasingly considered to be crucial for the prevention of diabetic macrovascular complications and postprandial hyperglycemia. The extent to which 1,5-AG levels predict variability is presently unclear.

## Future Direction and Concerns

One of the causes of diabetes is monogenic disorders of the â- cell (maturity onset diabetes of the young [MODY]).[15] In clinical practice distinguishing HNF1A- MODY and GCK -MODY, the most common types of MODY , from other common types of diabetes is difficult. But, measurement of serum 1,5- AG levels can be a novel test which would allow differentiation between not only type 1 and type 2 diabetes but discrimination of HNF1A from type 2 diabetes also.[16] This is because the level of 1,5-AG falls down than expected in the blood due to lower renal threshold for glucose [17] and the mutations in HNF1a are

also characterized by a low renal glucose threshold.[18] Hence, 1,5-AG could be an emerging biomarker for HNF1A- MODY and MODY subtypes.[19] This in turn will guide to correct diagnosis and also will help in defining etiology of diabetes.

Monitoring 1,5-AG levels in people with type 1 and type 2 diabetes could be helpful to determine if the blood glucose levels are under control or not. This test seems to be a promising one for monitoring glycemia in type 2 diabetes. This is because it is an index of post-prandial glucose level in T2D. This is especially important as post-prandial hyperglycemia is linked to cardiovascular diseases. It has been reported that cardiovascular diseases are associated with higher HbA1c levels in both men and women and that to a greater extent, postprandial blood glucose predicts the cardiovascular events. [13]Furtherresearch is required to establish a link between 1,5-AG levels and cardiovascular outcomes.

In general, diabetic patients, when they come to a hospital, measure only their fasting and post-breakfast values. But, what about post-lunch, post-dinner and even post-snack blood glucose levels? These are rarely measured and using SMBG to measure them may not be accurate. Not measuring post-meal values for every meal of the day may miss to quantify the overall burden of hyperglycemia.

The 1,5-AG, is a single fasting or non-fasting blood test, which manages to give an index of post-prandial glucose fluxes after every meal of the day over several days. Thus, in addition to the fasting blood glucose (which is a more steady value as compared to a single post-meal value), testing 1,5-AG may provide an additional tool to discover post-prandial hyperglycemia and thus guide therapy.

The use of 1,5-AG as a test raises several issues.[19-23] There are several limitations, and an emerging limitation is the lack of the test's efficacy in mirroring hyperglycemia when glucosuric drugs likeCanagliflozin and Dapagliflozin (SGLT-2 inhibitors) are consumed.[23] Diabetic patients when treated with alpha-glucosidase inhibitors like acarbose shows disparity between serum 1,5-AG levels and related glucose levels. Serum 1,5-AG level is lower in people treated with acarbose. Because of reduction in intestinal absorption of 1,5-AG.[20] Another limitation is the lack of established correlation between 1,5-AG cut-offs and diabetic microvascular and macrovascular complications.

There may be new, hitherto undiscovered advantage of the 1,5-AG test. For example, a new study documents its potential benefits in detecting glucose varaibility (dispite near normal HbA1c) after islet cenn transplantation. [22]Further studieswill determine how the science of 1,5-AG measurments will benefit clinical outcomes in subjects with diabetes worldwide. Overall, 1,5-AG is a promising innovation, and could pave the way to developing newer tools to ascertain hyperglycemia.

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***"Natural forces within us are the true healers of disease."***
— Hippocrates