

A1C (Hemoglobin A_{1c})

Introduction

Glycohemoglobin (GHb) of Hemoglobin A_{1c} (or A1C) is an important marker for diabetes care. The American Diabetes Association (ADA) recommends the measurement of A1C as standard medical care for a long-term assessment of glycemic control in patients with diabetes.¹

A1C reflects the average blood glucose level over the prior 2-3 months. As such, it accurately and reliably assesses the effectiveness of treatment and risk for development of acute and/or long-term chronic complications typically associated with sub-optimal diabetes control. Routine monitoring of A1C can improve patient compliance when used as part of a comprehensive treatment plan.

What is A1C?

Glucose is present in the blood and is freely permeable through the red blood cell membrane so the concentration of glucose inside the red blood cell is equal to the concentration in the plasma. Glucose binds to both serum proteins in the blood as well as the hemoglobin contained within the red blood cells through a non-enzymatic reaction. In this reaction the amount of glucose that is bound to a protein is directly dependent on the amount of glucose that is present. Once glucose binds to hemoglobin ('glycohemoglobin'), it remains there for the life of the cells, which may be up to 4 months. The higher the level of blood glucose that the hemoglobin is exposed to, the more glycohemoglobin will be present in the cells.

The three most common types of glycohemoglobin are A_{1a}, A_{1b}, and A_{1c}. Of these, glycohemoglobin A_{1c} represents the most prevalent species.²

The medical community has adopted the term 'A1C Test' to refer to all glycohemoglobin measurements if they have been standardized to reflect hemoglobin A_{1c} levels. A1C levels are expressed as: the amount of glycohemoglobin to the total hemoglobin.

Why Test?

The A1C test gives a reliable picture of how much glucose has been in the bloodstream during the past 2 to 3 months. Thus, A1C is a long-term measure of how well glucose levels have been controlled in a diabetic patient. Self-monitoring of glucose gives a snapshot of control at the time of the test, while the A1C test provides a bigger picture of glucose control over the past 2 to 3 months. Together, these tests represent whether the patient's blood glucose is under control. This is called 'glycemic control'.

DCCT and UKPDS

Two breakthrough studies conducted in the last decade, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have clearly demonstrated that improved glycemic control reduces the development and progression of several micro- and macrovascular complications in both type 1 and type 2 diabetes mellitus.^{3,4}

The DCCT, completed in 1993, study showed that maintaining blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes. In fact, it demonstrated that any sustained lowering of blood glucose helps, even if the person has a history of poor control. The DCCT also provided a large body of data relating A1C values to mean blood glucose.

Thus, the DCCT study set the stage for establishing specific diabetes treatment goals using A1C as an index of mean blood glucose.

The UKPDS, completed in 1998, showed results similar to the DCCT in patients with type 2 diabetes.

Benefits of Immediate A1C Testing

An immediate A1C result is an essential tool for physicians in their routine management of patients with diabetes mellitus. The A1C result available at the time of the visit can improve clinical decision-making.⁵⁻⁸ Specifically, it facilitates the identification of patients who are already appropriately controlled (A1C <7%) and helps to avoid further intensification of therapy in such patients.

The Cholestech GDX™ is a CLIA-waived A1C testing system for measuring A1C in less than five minutes using a drop of blood from a fingerstick. The GDX System provides the health professional with immediate information on the long-term glucose control of their patients, allowing them to implement management changes. Delayed patient feedback could lead to decreased patient compliance and delayed adjustment of hypoglycemic regimens.

Hemoglobin Variants

More than 700 characterized hemoglobin (Hb) variants have been reported, the majority of which are genetic mutations. Nearly 8% of African Americans carry the HbS trait and 2.3% carry HbC. In sub-Saharan Africa, prevalence of these two is up to one-third of all patients. HbE can be as high as 30% in Southeast Asia. Many

hemoglobinopathies, including sickle cell disease, homozygous HbC disease, HbSC disease, and β -thalassemia, frequently show increased amounts of minor Hb species, i.e. HbA₂ and HbF. HbF can reach 30% in individuals with hereditary persistence and 20% in β -thalassemia and sickle cell patients. Chemically modified Hbs may be chronically present in diabetic patients. Carbamylated Hb is the most commonly encountered of these.⁹ Facilities performing A1C testing should be aware of interferences produced in such assays from genetic variants such as HbS, HbC, and HbE and chemically modified derivatives such as carbamyl-Hb of hemoglobin.

Differences in Methods for A1C Measurement

A wide variety of methods are used to measure glycohemoglobin, including immunoassay, cation-exchange high performance liquid chromatography (HPLC), and affinity chromatography (i.e. boronate). Although all commercial methods include hemoglobin A1C in glycohemoglobin measurements, they vary in their ability to detect non-A1C glycohemoglobin. Immunoassay methods are variously susceptible to interference depending upon the selection of the antibody(s). Cation-exchange HPLC systems are however, designed to flag results that suggest variant interference in some, but not all, cases. In general, boronate affinity is essentially free of variant interference while cation-exchange chromatography is susceptible. Pathologic conditions affecting red cell half-life that may be present in diabetic patients can affect glycohemoglobin results, regardless of testing method.⁹

Analysis of clinical laboratory proficiency surveys for GHb measurement, conducted by the College of American Pathologists (CAP) in 1999, revealed that more than one-half of participating clinical laboratories use boronate affinity chromatography for determining GHb, either as A1C or as total GHb.⁹ Because different laboratories use different methods, practitioners should

familiarize themselves with the methodology of their local laboratory. Preferably a single laboratory should be used for all measurements for patients of a given physician to lessen confusion.

The Cholestech GDX System has virtually no interference from hemoglobin variants because the analyzer uses boronate affinity chromatography to separate the glycated hemoglobin fraction from the non-glycated fraction. Both fractions are measured and an algorithm converts the result into the percentage A1C in the sample.

Standardization, the NGSP

In April 1993, The American Association for Clinical Chemistry (AACC) Standards Committee established a glycohemoglobin Standardization Subcommittee. Since there were a variety of different analytical methods for measuring GHb with each method reporting slightly different results there was a need to standardize the methods. The DCCT has established relationships of GHb values to mean blood glucose and to risks for the development of chronic diabetic complications. The goal of the subcommittee was to develop a plan for GHb standardization that would ultimately allow individual clinical laboratories to relate their GHb test results to those of large-scale studies such as the DCCT. The result was the National Glycohemoglobin Standardization Program (NGSP), administered by a network of reference laboratories in the US and Europe.³

The purpose of the NGSP is to standardize glycohemoglobin test results so that clinical laboratory results are comparable to those reported in the DCCT where risk for vascular complications have been established. The NGSP certifies manufacturers' test methods. If a manufacturer's test method meets stringent requirements for accuracy and precision, the method is certified by the NGSP to provide results that are traceable to the DCCT. NGSP certification requires annual renewal to

ensure that methods continue to meet requirements. Information on the NGSP is available on the web at <http://www.missouri.edu/~diabetes/ngsp.html>. Accuracy and precision of the Cholestech GDX A1C test met NGSP requirements for certification in two successive years. GDX A1C results are therefore traceable to the DCCT.

ADA Clinical Practice Recommendations

The American Diabetes Association (ADA) offers clinical practice recommendations for the management of diabetes. The ADA recommends A1C testing as part of the initial work-up of a diabetic patient to document the initial level of glycemic control. In addition, it is recommended that bi-annual (or semi-annual) testing for all diabetics is performed and quarterly A1C testing for those diabetics whose therapy has changed or who are not meeting their glycemic goals.¹⁰

Significant scientific evidence for the current treatment goals has accumulated over the past decade. The results of the DCCT showed that an average A1C of 7.2% resulted in a 50-70% reduction in risk of the development or progression of retinopathy, nephropathy, and neuropathy in people with type 1 diabetes while the UKPDS showed that type 2 diabetics can achieve a 35% reduction in risk of nephropathy for each percentage point that their HbA_{1c} levels are decreased. The UKPDS has also provided strong support for the American Diabetes Association's position that vigorous treatment of diabetes can decrease the morbidity and mortality of the disease by decreasing its chronic complications. The reduction in risk of these complications correlated continuously with the reduction in A1C indicating that any decrease in A1C toward normal is likely to achieve better outcomes.¹¹ The ADA recommends that the goal of therapy should be an A1C result of <7% and that physicians should reevaluate and, in most cases, significantly change the treatment regimen in patients with A1C test results consistently >8%. Again, these

specific A1C values apply only to assay methods that are certified as traceable to the DCCT reference method.

Glycemic Control as Recommended by the American Diabetes Association

A1C

Normal	<6%
Goal	<7%
Additional action suggested*	>8%

* Values above/below these levels are not "goals" nor are they "acceptable" in most patients. They are an indication for a significant change in the treatment plan. "Additional action suggested" depends on individual patient circumstances.¹

Note: The medical literature uses many different terms to describe A1C. Glycohemoglobin is short for 'glycated' or 'glycosylated' hemoglobin and is often abbreviated as 'GHb'. Because the laboratory methods for GHb differ, tests may also be described by the more or less specific hemoglobin species they measure, e.g. hemoglobin A₁ or hemoglobin A_{1c}. When properly standardized, all of these different methods are very highly correlated. It is now common to refer to them all collectively as 'A1C', though GHb is considered the more scientifically accurate term.

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