Sickle Cell Trait and Other Hemoglobinopathies and Diabetes: Important Information for Physicians

The hemoglobin A1C (A1C) test can lead to false outcomes resulting in over-treatment or under-treatment of diabetes in people with inherited hemoglobin variants, also called hemoglobinopathies. Hemoglobin S and E are prevalent variants in people of African, Mediterranean, or Southeast Asian descent. These variants interfere with some A1C tests—both laboratory and point-of-care tests. If A1C tests are at odds with blood glucose monitoring results, interference should be considered. Reliable A1C tests, in which hemoglobin variants do not cause interference, are available. More information is available at* www.ngsp.org, *the National Glycohemoglobin Standardization Program. A1C should be measured at least twice annually to assess control of diabetes but should not be used to diagnose diabetes.

The hemoglobin A1C (A1C) test can lead to false outcomes resulting in over-treatment or under-treatment of diabetes in people with inherited hemoglobin variants, also called hemoglobinopathies. Although the A1C test is not recommended for diagnosis of diabetes, when it has been used for diagnosis in people with hemoglobin variants, the test has yielded false results. People of African, Mediterranean, or Southeast Asian descent are at increased risk for having hemoglobin variants.

Physicians and clinical laboratories need to be aware of the effects of hemoglobin variants upon A1C test results. The National Glycohemoglobin Standardization Program (NGSP) *(www.ngsp.org)* provides information about which assay methods are affected by specific hemoglobinopathies, permitting choice of an appropriate assay method for patients with hemoglobinopathies.

When to Suspect that a Patient with Diabetes Has a Hemoglobinopathy

People who carry one gene for a hemoglobinopathy are often unaware. Several situations may indicate the presence of a hemoglobinopathy:

- when results of self-blood-glucose monitoring have a low correlation with A1C results
- when an A1C result is different than expected
- when an A1C result is more than 15 percent
- when a patient's A1C test result is radically different from a previous test result following a change in laboratory A1C methods

Diagnosis of Hemoglobinopathies

Carrier state can easily be detected by hemoglobin electrophoresis. Most states now screen for common hemoglobin variants in newborns and report results. In addition, pre-pregnancy genetic testing and prenatal screening are done in some high-risk populations or in women with a family history of a variant. Screening may also be done in parents of children with identified variants and patients with red blood cell abnormalities, such as unexplained anemia.

National Institute of Diabetes and Digestive and Kidney Diseases

NATIONAL INSTITUTES OF HEALTH

U.S. Department of Health and Human Services

Statistically speaking…

Hemoglobin S and C

African Americans have an increased risk of inheriting sickle cell trait, the condition in which people have both hemoglobin A (HbA), the usual form of hemoglobin, and hemoglobin S (HbS), a variant. They also are at risk for having hemoglobin C (HbC), another variant. About one in 12 African Americans has sickle cell trait. African Americans are nearly twice as likely to have diabetes as Caucasians of similar age. About 13 percent of African Americans aged 20 years or older have diabetes.[1] Therefore, many African Americans have both diabetes and sickle cell trait.

Hemoglobin E

People of Southeast Asian descent are at risk for having hemoglobin E (HbE), another hemoglobin variant. Prevalence of diabetes in Asian Americans varies among subpopulations. Studies have shown that some groups of Asian Americans in the United States are 1.5 to 2 times as likely to have diabetes as Caucasians of similar age.[1]

---

[1] National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH). National diabetes statistics. Available at: www.diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm. Posted November 2005. Accessed July 5, 2007.

The A1C Test

The American Diabetes Association (ADA) does not recommend use of the A1C test for diagnosis of diabetes. Instead, the fasting plasma glucose test should be used to diagnose diabetes in children and nonpregnant adults. The ADA recommends use of the A1C test as part of the initial assessment and in continuing care of people with diabetes. Physicians should perform the A1C test

- at least twice a year in patients who are meeting treatment goals and have stable glycemic control
- quarterly in patients not meeting treatment goals or when changes are made in therapy

In addition, point-of-care testing for A1C can help in making timely decisions about changes in therapy.

ADA Targets for the A1C Test

Group	Target
Patients in general	Less than 7 percent
Individual patients	As close to normal as possible—less than 6 percent—without significant hypoglycemia
Patients with a history of severe hypoglycemia, those with limited life expectancies, very young children, older adults, and patients with comorbid conditions	Less stringent goals

Technically speaking…

The A1C test measures the amount of glycated hemoglobin in the blood, which indicates average blood glucose levels over the preceding 2 to 3 months. Also called glycated hemoglobin or glycohemoglobin, the A1C test is based on the addition of glucose to hemoglobin over the typical 120-day life span of a red blood cell. Formation of glycated proteins is proportional to the concentration of glucose in the blood. The A1C test helps gauge risk of long-term complications; studies have demonstrated substantial reductions in long-term complications of diabetes with lowering of A1C.

Effect of Hemoglobinopathies on A1C Test Results

With some assay methods, A1C tests in patients with hemoglobinopathies result in falsely high outcomes, overestimating actual average blood glucose levels for the previous 2 to 3 months. Physicians may then prescribe more aggressive treatments, resulting in increased episodes of hypoglycemia. Some assay methods used with some hemoglobinopathies may result in falsely low outcomes, leading to undertreatment of diabetes.

The A1C test is not recommended for diagnosis of diabetes in the general population because it is not sufficiently sensitive. Also important, in patients with hemoglobinopathies, results may be falsely elevated, so physicians may erroneously conclude a patient has diabetes. Confirmation with a fasting blood glucose is required for a diagnosis of diabetes to prevent inappropriate treatment decisions.

Hemoglobinopathies

Hemoglobin molecules in red blood cells transport and distribute oxygen to cells throughout the body. Hemoglobin is composed of heme—the portion of the molecule containing iron—and globin—a protein made up of amino acid chains.

Hemoglobin variants occur when mutations in the globin genes result in changes in the amino acids of the globin protein. Hundreds of variants have been identified; a small number of variants are common and have clinical significance. Hemoglobin variants are inherited in an autosomal recessive manner.

Common Types of Hemoglobinopathies

Table 1 summarizes the affected populations, prevalence, and outcomes of common hemoglobinopathies. These hemoglobinopathies may either falsely raise or lower A1C results, depending on the variant and the assay method.

People who are heterozygous for a variant are said to have a trait or to be carriers and are usually asymptomatic. Those who are homozygous generally have a disease condition. Hemoglobin SC (HbSC) is a compound heterozygous condition, meaning that the patient has inherited genes for two variants: HbS from one parent and HbC from the other.

Table 1. Common Hemoglobinopathies: Populations Affected, Prevalence, and Outcomes

Hemoglobin (Hb) Variant	Populations Affected	Prevalence (in the United States unless otherwise noted)	Outcome with One Abnormal Gene and One Normal Gene (Heterozygous State)	Outcome with Two Abnormal Genes (Homozygous State)
Hemoglobin S (HbS)	African Americans Hispanic Americans/Latinos Also found in East India, the Mediterranean, and the Middle East	About one in 12 African Americans has sickle cell trait [1] About one in 100 Hispanic Americans/Latinos has sickle cell trait [2] Sickle cell anemia occurs in one of every 500 African American births [1] Sickle cell anemia occurs in one of every 1,000 to 1,400 Hispanic American/Latino births [1]	Sickle cell trait (also called HbAS): usually asymptomatic	Sickle cell anemia (also called HbSS disease): sickled red blood cells that interfere with circulation and decrease life span of red blood cells; can result in hemolytic, splenic sequestration, and aplastic crises and multiple complications

Hemoglobin (Hb) Variant	Populations Affected	Prevalence (in the United States unless otherwise noted)	Outcome with One Abnormal Gene and One Normal Gene (Heterozygous State)	Outcome with Two Abnormal Genes (Homozygous State)
Hemoglobin C (HbC)	African Americans People of West African descent	About 2.3% of African Americans have HbC trait [3]	HbC trait (also called HbAC): asymptomatic	HbC disease (also called HbCC disease): mild hemolytic anemia, mild to moderate enlargement of the spleen
Hemoglobin E (HbE)	Asian Americans, especially those of Southeast Asian descent Common in Cambodia, Indonesia, Laos, Malaysia, Thailand, and Vietnam. Also seen in southern China, India, the Philippines, and Turkey	Prevalence of HbE may be 30% in Southeast Asia [3]	HbE trait (also called HbAE): asymptomatic	HbE disease (also called HbEE disease): mild hemolytic anemia, microcytosis, and mild enlargement of the spleen
Hemoglobin SC (HbSC)	African Americans and people of West African descent Also found in East India, the Mediterranean, and the Middle East		N/A	HbSC disease (also called sickle-hemoglobin C disease): mild hemolytic anemia and moderate enlargement of the spleen; may have blocking of blood vessels as in sickle cell anemia but milder symptoms
Hemoglobin F (HbF) elevated	Occurs in patients with hereditary persistence of fetal hemoglobin, sickle cell anemia, severe anemias, leukemia, and other conditions	About 1.5% have more than 2% HbF but some groups may have concentrations as high as 12% [3]	N/A	Those with elevated HbF and sickle cell anemia may have a milder form of sickle cell anemia

[1] National Heart, Lung, and Blood Institute, NIH. Sickle cell anemia. Available at: www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_All.html. Posted May 2007. Accessed June 27, 2007.

[2] National Human Genome Research Institute, NIH. Learning about sickle cell disease. Available at: www.genome.gov/10001219. Posted February 2007. Accessed July 3, 2007.

[3] Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. *Clinical Chemistry*. 2001;47(2):153–163.

Information about Assay Methods for Patients with Hemoglobinopathies

The NGSP provides a table on the NGSP website at *www.ngsp.org/prog/index2.html* describing the effects of frequently encountered Hb variants and derivatives on glycohemoglobin measurement for more than 25 assay methods. The NGSP website also includes a list of references for the information summarized in the table.

According to the NGSP, as of July 2007, 14 percent of laboratories are using assay methods with clinically significant HbAS interference; 13 percent use methods with clinically significant HbAC interference. However, after upcoming changes in reagents expected to be complete by the end of 2008, only about 5 percent of laboratories will be using methods resulting in significant HbAS or HbAC interference.

Alternative Tests

Physicians may wish to consider using other measures of average blood glucose levels, such as the fructosamine test, also called glycated serum protein or glycated albumin, with patients who have hemoglobinopathies where an accurate A1C result cannot be obtained. Serum proteins show average glucose levels over a much shorter period of time than the A1C test, usually about 2 to 3 weeks. Moreover, the fructosamine test is not standardized and the relationship of results of this test to glucose levels or risk for complications has not been established.

Anticipated Changes in A1C Reporting

A plan is under way to change how A1C results are reported. Final details will be determined based on the results of a study in progress. Results may be provided in the following ways:

- with the current name and units—as a percentage
- with the current name and as mmol hemoglobin A1C/mole hemoglobin
- as A1C derived average glucose, also called ADAG, in mg/dL or mmol/L—if study results confirm acceptability of this option

Other Conditions that Can Affect A1C Test Results

A number of other conditions, such as those that reduce the life span of red blood cells, can affect A1C results. Recent acute blood loss or hemolytic anemia can falsely lower A1C results. Intake of large amounts of vitamin C or vitamin E can falsely lower or elevate results. Iron deficiency anemia can falsely elevate results.

Points to Remember

- Hemoglobinopathies are inherited hemoglobin variants caused by globin gene mutations.
- People of African, Mediterranean, or Southeast Asian descent are particularly at risk for having hemoglobin variants.
- Hemoglobin variants may confound results of the A1C test, which indicates average blood glucose levels over the preceding 2 to 3 months.
- False A1C test results can lead to false diagnosis or over-treatment or under-treatment of diabetes in people with hemoglobinopathies.
- Information to assist in selecting the best assay methods is available from the National Glycohemoglobin Standardization Program (NGSP).
- The most common hemoglobin variants include hemoglobin S, C, and E.
- People who are homozygous for a hemoglobin variant may have a disease condition—for example, those who are homozygous for the hemoglobin S variant have sickle cell anemia. Those who are heterozygous for a variant are said to have a trait or to be carriers and are usually asymptomatic.
- A booklet for people with diabetes about hemoglobin variants and the A1C test, *For People of African, Mediterranean, or Southeast Asian Heritage: Important Information about Diabetes Blood Tests*, is available from the National Diabetes Information Clearinghouse or online at *www.diabetes.niddk.nih.gov/dm/pubs/traitA1C*.

For More Information

National Glycohemoglobin Standardization Program
Internet: www.ngsp.org

American Diabetes Association
1701 North Beauregard Street
Alexandria, VA 22311
Phone: 1–800–DIABETES (342–2383)
Fax: 703–549–6995
Email: AskADA@diabetes.org
Internet: www.diabetes.org

National Heart, Lung, and Blood Institute Health Information Center
P.O. Box 30105
Bethesda, MD 20824–0105
Phone: 301–592–8573
Fax: 240–629–3246
Email: nhlbiinfo@nhlbi.nih.gov
Internet: www.nhlbi.nih.gov

You may also find additional information on this topic using the following databases:

The NIDDK Reference Collection is a collection of thousands of materials produced for patients and health care professionals, including fact sheets, brochures, and audiovisual materials. Visit *www.catalog.niddk.nih.gov/resources*.

MedlinePlus brings together a wealth of information from the National Library of Medicine, the National Institutes of Health, and other government agencies and health-related organizations. MedlinePlus offers easy access to medical journal articles, a medical dictionary and medical encyclopedia, health information in Spanish, hospital and physician directories, drug and supplement lists, interactive patient tutorials, links to hundreds of clinical trials, and the latest health news. Visit *www.medlineplus.gov*.

The U.S. Government does not endorse or favor any specific commercial product or company. Trade, proprietary, or company names appearing in this document are used only because they are considered necessary in the context of the information provided. If a product is not mentioned, the omission does not mean or imply that the product is unsatisfactory.

This publication may contain information about medications used to treat a health condition. When this publication was prepared, the NIDDK included the most current information available. Occasionally, new information about medication is released. For updates or for questions about any medications, please contact the U.S. Food and Drug Administration at 1–888–INFO–FDA (463–6332), a toll-free call, or visit their website at *www.fda.gov*. Consult your doctor for more information.

National Diabetes Information Clearinghouse

1 Information Way
Bethesda, MD 20892–3560
Phone: 1–800–860–8747
Fax: 703–738–4929
Email: ndic@info.niddk.nih.gov
Internet: www.diabetes.niddk.nih.gov

The National Diabetes Information Clearinghouse (NDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health of the U.S. Department of Health and Human Services. Established in 1978, the Clearinghouse provides information about diabetes to people with diabetes and to their families, health care professionals, and the public. The NDIC answers inquiries, develops and distributes publications, and works closely with professional and patient organizations and Government agencies to coordinate resources about diabetes.

Publications produced by the Clearinghouse are carefully reviewed by both NIDDK scientists and outside experts. This publication was reviewed by Charles M. Peterson, M.D., M.B.A., Director, Division of Blood Diseases and Resources at the National Heart, Lung, and Blood Institute, National Institutes of Health, and Randie R. Little, Ph.D., National Glycohemoglobin Standardization Program, University of Missouri School of Medicine.

This fact sheet is also available at *www.diabetes.niddk.nih.gov*.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIH Publication No. 08–6287
November 2007