Evaluation of diabetic marker Hba1c and anemia in the context of kidney disease

By Priya Sivaraman, PhD, Nilam Patel, MT(ASCP)SH, and Anita Weissman, BS, MA

Each year, more than 100,000 people in the United States are diagnosed with kidney failure, the final stage of kidney disease. The most common cause is diabetes, accounting for nearly 44 percent of new cases. Often, a consequence of kidney disease is anemia. This occurs when kidneys fail to generate enough erythropoietin hormone to trigger adequate red blood cell production. For decades, clinicians have successfully used the hemoglobin A1c (HbA1c or A1C) assay to monitor long-term blood glucose control for patients with chronic diabetes. More recently, researchers have begun to use the HbA1c assay as a potential diagnostic marker for diabetes complications such as kidney disease.

The HbA1c test measures average plasma glucose—hemoglobin in a red blood cell that was combined with glucose over the previous eight to 12 weeks. The higher the HbA1c value, the greater the risk that the diabetes patient will develop kidney disease and, perhaps, anemia, a common consequence of renal disease. However, a chemically modified derivative of hemoglobin called carbamylated hemoglobin (CHb) can affect the accuracy of the HbA1c test results. Studies have shown that the formation of CHb due to abnormal urea concentration is linked to both the severity and the duration of renal failure. Research findings have inspired conflicting viewpoints on the efficacy of HbA1c test results in the presence of CHb and on the level of CHb it takes to affect results. This article explores the links between diabetes and renal failure. It discusses what research has discovered about the effect of CHb on HbA1c testing. Finally, it shows how testing technology has improved to ensure HbA1c testing accuracy.

Kidney disease and diabetes

Nearly 24 million people in the U.S. have diabetes, and nearly 180,000 people are living with kidney failure as a result of diabetes. Poor blood glucose control is among the key factors that can contribute to the onset of diabetic kidney disease. Other factors include family history, race (African-Americans, Hispanics, and some Native American tribal members are more prone), obesity, and poor blood pressure control. The risk of developing chronic kidney disease (CKD) is similar in patients with type 1 or type 2 diabetes, with about 30 percent of either group developing some form of kidney disease. In diabetic patients with end-stage renal disease, erythrocyte lifespan tends to be decreased. This may result in part from iron deficiency anemia, frequent transfusions, or other effects of kidney disease on erythrocyte survival.

Benefits of the HbA1c test

The A1C assay has been used for the management of chronic diabetes for decades and more recently has been recommended for its role in diagnosis. The A1C test provides clinicians with an overall picture of the average blood sugar levels over the previous two to three months. The A1C values provide clinicians with a simple and quick method of monitoring diabetes control and can be used to adjust therapy as needed.

In recent years, several methods have been introduced to improve HbA1c testing accuracy. Some studies on the effects of CHb from varying degrees of renal insufficiency have demonstrated that the HbA1c assay is affected by CHb. These studies have prompted improvements in HbA1c testing technology to yield cyanate ions. The cyanate assay can theoretically provide accurate HbA1c values even in the presence of CHb. However, several methods have been improved to have better resolution of HbA1c and other hemoglobin adducts. Neuer ion-exchange HPLC methods in particular have improved the resolution between HbA1c and other hemoglobin adducts so that peaks such as CHb are clearly demarcated from the HbA1c peak in the chromatogram. Methods such as immunoadsorption, boronate affinity chromatography, and enzymatic methodologies have improved the detectability of hemoglobin adducts other than HbA1c.

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Some studies on the effects of CHb from varying degrees of renal conditions have indicated that the CHb in the methods used showed no apparent effect on A1c values at high thresholds of CHb levels. That said, there is an ongoing debate about the most useful way to monitor glycemic control in chronic renal failure (CRF) patients.

CKD and anemia

In patients diagnosed with both diabetes and CKD, there is a high risk for anemia, especially among those who require dialysis. Anemia is almost universal in end-stage renal disease (ESRD), because of insufficient production of erythropoietin by non-functioning

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kneys. To screen and manage patients at risk for anemia, prac-
titioners can use the comprehensive reticulocyte panel as part of expanded CBC results. The additional data includes absolute ret-
iculocyte counts, reticulocyte percentage, immature reticulocyte fraction (IRF), and reticulocyte hemoglobin equivalent (RET-He). RET-He is a measurement of the hemoglobin content of the de-
veloping reticulocyte population. Unlike traditional iron tests such as serum iron, ferritin, and TSAT, which are affected by inflam-
mation, RET-He is not sensitive to interference from underlying inflammatory conditions. Pathophysiological mechanisms of ane-
mia can be elucidated and used to justify specific therapy choices. Reticulocyte counts represent the erythropoietic contributions, while reticulocyte hemoglobin content represents iron-dependent hemoglobinization.

The RET-He is included in key guidelines that drive the national and global anemia management of kidney disease. These guiding principles include Kidney Disease Outcome Quality Initiative Guidelines (KDOQI) published in 2006; Kidney Disease: Improving Global Outcomes Guidelines (KDIGO) published in 2012; and most recently NICE (National Institute for Health and Care Excellence) 2015 recommendations. The use of RET-He in challenging patients is extremely helpful because it can alert practitioners to the presence of iron deficiency anemia when traditional tests are inconclusive. It can also help assess the effectiveness of treatment earlier than traditional parameters.17

Lab testing and automation

Automation is a key focus by laboratories today. Laboratories im-
plement or explore automation to reduce errors, improve clinical data turnaround time, and reduce overall operational costs. Test-
ing solutions that provide clinical data to assess and manage this patient population are available as stand-alone work stations or as a single workstation.

Most A1C methods provide accurate results in CRF patients; methods such as ion-exchange HPLC can provide the ability to de-
tect the presence of CHB that is elevated in CRF patients. Auto-
mation can provide both HbA1c (using ion-exchange HPLC) and RET-He through the use of a single sample from the patient. In
addition, the single workstation automation system includes de-
cision logic software to maximize clinical data turnaround time. Decision logic software allows filtering abnormal results (those that need further attention) from normal/auto-verified (those that will be automatically released to LIS and directly to patient chart) using instrument-specific rule set.

Thus, patients who exhibit peak abnormalities are quickly and automatically filtered (through the activation of rules) and identi-
sified, so that the laboratorian can focus and follow up promptly. Laboratories that have applied this type of automation can realize benefits with workstation elimination, reduction in hands-on time with testing, and improvement in overall turnaround time.

Clinicians have options that can help to diagnose and manage disease states. The HbA1c assay, used successfully by clinicians for diabetes control, is a valuable tool in diagnosis of diabetes. The higher a diabetes patient’s measured HbA1c value, the greater the risk of developing diabetes-related kidney disease. An accurate A1C result is important, especially in the presence of CHB that is elevated in kidney disease patients. It is important that clinician and laboratory be aware of methods that provide an accurate A1C in the presence of CHB for proper patient care.18 The risk of de-
veloping anemia in kidney disease patients is great, and proper assessment and management of this condition is also important. A comprehensive retic panel with RET-He provides better reliability versus traditional anemia testing panels, enabling clinicians to de-
termine the best course in overall care for these patients.19 RET-He, measured at the cellular level, reflects change within three to five
days of therapy, and is not impacted by inflammatory processes. National and global kidney organizations have recognized the value of RET-He in anemia management and have included the parameter in key guidelines.18-21 Early screening for iron deficiency anemia and efficient disease management can promote patient outcomes and reduce healthcare costs.

REFERENCES

1. USRDS 2007 Annual Data Report. United States Renal Data System. National Insti-


14. Weykamp C, John WS, Mosca A. A review of methods for measuring hemoglo-


Priya Sivaraman, PhD, serves as a Senior Product Manager, Clinical Diagnostics, for Bio-Rad Laboratories Inc. She is responsible for education and awareness of diabetes and hemoglobin disorders in the U.S.

Nilkam Patel, MT(ASCP)SH, serves as a Senior Product Manager for Sysmex America. She is responsible for understanding the needs and applicability of automation within the various customer market segments of North America.

Anita Weissman, BS, MA, is a communications strategy consultant to healthcare, biotechnology, and medical device companies. As a communications consultant to the Community Oncology Alliance, she played a key role in formulating national cancer care policy and regulatory action.

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