CLINICAL VIGNETTE

Potential Pitfalls of Hemoglobin A1c Measurement in Diagnosis of Diabetes

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Case Presentation

A 48-year-old obese Hispanic female, with history of hypertension, hyperlipidemia, chronic iron deficiency anemia (secondary to heavy menstrual bleed), and recently diagnosed diabetes mellitus type II during hospitalization for NSTEMI (s/p coronary artery bypass graft) presents to establish care and discuss diagnosis of diabetes.

Patient questioned if she truly has diabetes as she rarely eats sweets. She also wanted to stop metformin as she sometimes feels lightheadedness right after she takes it. No associated diaphoresis, fatigue, weakness, shakiness, palpitations. No history of polyuria, polydipsia, polyphagia, numbness/tingling of extremities.

Prior to NSTEMI admission, patient was not on iron supplementation, had no blood transfusions and was not taking any supplements. Her family history was notable for premature coronary artery disease in mother and diabetes type 2 in father.

Physical Exam

BP 157/79, pulse 67, BMI 30 kg/m²
HEENT: no conjunctival pallor
CV: normal rate, regular rhythm, no murmur
Extremity: Trace bilateral lower extremity edema
Skin: no petechiae, purpura

Labs from NSTEMI admission included: hemoglobin A1c 6.8, hemoglobin 8.0, MCV 70.1(L) iron 16(L), TIBC 385, iron sat 4(L), ferritin 5(L), TSH 5.2(H), fT4 0.95(n), blood glucose 97, creatinine 0.7, total protein, albumin 4.2

Discussion

In 2010, the American Diabetes Association (ADA) added hemoglobin A1c as a diagnostic criterion for diabetes.[1] As hgb-A1c is convenient to obtain as compared to fasting blood glucose or oral glucose tolerance test, it is frequently ordered to diagnose diabetes. It is important to recognize clinical scenarios and interfering factors that can impact results and lead to over or under diagnosis of diabetes.

Hgb-A1c is a measure of the percentage of hemoglobin with glucose attached and reflects the average glucose exposure integrated over half-life of hemoglobin in red blood cell. Therefore, the level of A1c is influenced by red blood cell survival. Low red blood cell turnover can cause high A1c value in relation to mean blood glucose. Low turnover results in a disproportionate number of older red blood cells as seen in vitamin b12 deficiency anemia, folate deficiency anemia and iron deficiency anemia.

On the other hand, when red cell turnover is high, we expect falsely low hemoglobin A1c in relation to mean blood glucose level. This can be seen in chronic hemolysis such as thalassemia, G6PD deficiency; advanced chronic kidney disease, patients on dialysis, and patients treated with iron, vitamin b12, folate, or receiving erythropoietin.[2-6]

Hemoglobin variants are another less common cause of poor hgb-A1c values. The NGSP website (http://www.ngsp.org) has comprehensive information on hemoglobin variant interference with A1c measurement.

There are also racial and ethnic difference in hgbA1c measures. Several studies have reported higher A1c values in Hispanic American, African American and Asian American when compared to Caucasian American with similar blood glucose concentrations. These differences are small, approximately 0.3 to 0.4 percentage point difference in A1c.[7-13]

Our patient had chronic iron deficiency anemia, so the A1c of 6.8 may have been falsely elevated. The patient is also Hispanic with potential for slight elevation as compared to Caucasian norms. Thus, the A1c alone is not the ideal diagnostic test. This was reflected in the normal blood glucose of 97 on admission.

Management

For this patient, fasting and postprandial glucose measurements were monitored and oral glucose tolerance test will be obtained when patient is stable. These would not be impacted by chronic anemia with low red cell turnover.

Two additional lab tests can help support a diagnosis of diabetes, however are not used as diagnostic criteria. Serum fructosamine level and glycated albumin levels can be useful in the setting of abnormal cell turnover. The values from either test correlate with mean blood glucose values over 2-3 weeks. This relationship is only reliable with normal serum protein levels. Low serum protein results in falsely low fructosamine or

glycated albumin levels as with protein losing enteropathy and nephrotic syndrome.

Fructosamine level of 266-312mmol/L are approximately equivalent to A1c of 7 percent.[14-16] Glycated albumin values of 16-22 percent are also approximately equivalent to A1c of 7 percent.[14,15,17]

When patient presented she had been on metformin for several months and questioned if she truly had diabetes. She was scheduled to return for follow up hemoglobin A1c, serum fructosamine, fasting blood glucose and hemoglobin level.

Conclusion

Hemoglobin A1c is a commonly used to diagnose diabetes. It is impacted by improperly interpreted red cell turnover and ethnicity which can cause under or over diagnosis of diabetes.

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