South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Endocrine system

EVIDENCE SUMMARY:
Date: October 2017

Question: Should HbA1C be used as a diagnostic test for diabetes mellitus?

The current guidelines by the American Diabetes Association[1]address the diagnostic utility of fasting plasma glucose, 2-hour plasma glucose value after 75g oral glucose tolerance test, and HbA1C. According to these guidelines, unless there is a clear clinical diagnosis (patient in a hyperglycaemic crisis or with classic symptoms of hyperglycaemia and a random plasma glucose ≥11.1 mmol/L), a second test is required for confirmation. HbA1C has several advantages, including greater convenience (fasting not required), greater pre-analytical stability, and less day-to-day perturbations during stress and illness. These advantages may be offset by the lower sensitivity of HbA1C at the designated cut point, greater cost, limited availability, and the imperfect correlation between HbA1C and average glucose in certain individuals. National Health and Nutrition Examination Survey(NHANES) data indicated that an HbA1C cut point of≥6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥ 7.0 mmol/L.[2] When using HbA1C to diagnose diabetes, it is important to recognize that it is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact haemoglobinglycation independently of glycemia including age, race/ethnicity, and anaemia/haemoglobinopathies.

Race/ethnicity may influence HbA1C levels independently of glycaemia. A study done to look at the racial and ethnic differences in HbA1C among individuals with impaired glucose tolerance found that HbA1C levels were higher among U.S.A. racial and ethnic minority groups after adjustment for factors likely to affect glycaemia. Among patients with impaired glucose tolerance, HbA1C may not be valid for assessing and comparing glycaemic control across racial and ethnic groups or as an indicator of health care disparities.[3]A recent genome-wide association study looked specifically at a number of HbA1C-associated loci and tested the effect of genetic risk-scores comprised of erythrocytic or glycaemic variants on incident diabetes prediction and on prevalent diabetes screening performance.[4] Their findings included that in African Americans, the X-linked *G6PDG202A* variant (T-allele frequency 11%) was associated with an absolute decrease in HbA1C of 0.81%-units (95% CI 0.66–0.96) per allele in hemizygous men, and 0.68%-units (95% CI 0.38–0.97) in homozygous women. The *G6PD* variant may have caused approximately 2% (*N* = 0.65 million, 95% CI 0.55–0.74) of African American adults with T2D to remain undiagnosed when screened with HbA1C. They concluded that screening with direct glucose measurements, or genetically-informed HbA1C diagnostic thresholds in people with G6PD deficiency, may be required to avoid missed or delayed diagnoses.

In conditions associated with increased red blood cell turnover, such as pregnancy (second and third trimesters), haemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only blood glucose criteria should be used to diagnose diabetes.[1]Interpreting HbA1C levels in the presence of certain haemoglobinopathies may be problematic. For

patients with an abnormal haemoglobin but normal red blood cell turnover, such as those with the sickle cell trait, an HbA1C assay without interference from abnormal haemoglobins should be used.

In conclusion, it is evident that there are several factors that may influence the validity of using HbA1C to diagnose diabetes. From the current evidence it would appear that data is conflicting regarding the race/ethnic influence on HbA1C and it should therefore not be used in a population such as ours where it is not appropriately validated to diagnose diabetes. The current standard treatment guidelines do not advocate its use for the diagnosis of diabetes. It is recommended that due to the cost related to the test and the above mentioned findings, HbA1C not be used as a primary diagnostic modality in South Africa.

Summary prepared by Dr R Griesel.
Affiliation: University of Cape Town: Pharmacology Department; Adult Hospital Level Committee (2017-2018)
Conflicts of interest: None

References

1. American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care 2017;40(Suppl. 1):S11–S24.
2. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. Diabetes Care 2010;33:562–568.
3. Herman WH, Ma Y, Uwaifo G, et al. Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457.
4. Wheeler E, Leong A, Liu CT, et al. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. PLoS Med. 2017 Sep 12;14(9):e1002383