Factors Modulating Blood HbA1C Level and Diabetic Retinopathy

Kinjalka Ghosh1, Kanjalka Ghosh2
1Assistant professor Department of Biochemistry, KEM Hospital, Parel, Mumbai 400012, Maharashtra; 2Director, Institute of Immunohaematology, Mumbai, Maharashtra

Sir,

Requirement of different cut-off values of HbA1c for different racial1,2 or even different ethnic group deserves important introspection and discussion. Retinopathy is one of the important complication of diabetics, however the prevalence of this complication is not only dependent on degree of control of hypertension, viscosity of blood, ischaemic pathology in the retinal vasculature and overall other hormonal milieu like growth hormone levels.

Patients with unilateral constriction of carotid artery prevents development of diabetic retinopathy in that eye supplied by stenotic vessel.3 Certain unrelated conditions like Hb S-C disease, sickle cell anemia, hyperviscosity syndrome due to paraproteins, post-retinal venous occlusion produce some of the retinal pathology like diabetic retinopathy eventhough none of the above mentioned condition are associated with diabetes.

Three percent of healthy NHANES III population showed lesion resembling diabetic retinopathy. The salutary effect of photocoagulation shows that retinal ischaemia is a predominant cause of retinal vascular change in diabetics mellitus.

HbA1C level in the blood on the other hand depends on levels of hyperglycaemia and period through which hyperglycaemia lasts. This level is also dependent upon mean red cell life-span, so that HbA1C levels are reduced in haemolytic states. Moreover, structural haemoglobinopathy like HbS, HbC etc. are glycosylated but on HPLC based techniques for measurement of HbA1C level may not quantitate variant hemoglobinics which is glycosylated. Variant Hb like HbS may not be glycosylated at the same rate as adult Hb levels. HbS also alters the oxygen dissociation curve of Hb and shifts the curve to right as a result more oxygen is available to retina and this property is likely to have opposite effect on retinopathy. Black population has higher prevalence of haemoglobinopathies, essential hypertension and probably also has less tight glycaemic control.4

Hence there are multiple reasons why Asians, Caucasians and black races may have different values of blood HbA1C levels above which retinopathy risk and severity of diabetes increases.

Even the genetic determinants and environmental conditions may vary greatly amongst different populations in the world leading to different reference ranges of this haemoglobin derivative.

In India haemoglobinopathies like HbS, HbD and HbE genes are present in upto 40% of tribal population of central India, Punjabi population across the country and upto 40% population of Northeast and eastern parts of India respectively.5 This means in a large number of patients HPLC based HbA1c will not correcty reflect the glycosylation status of the haemoglobin molecule. Moreover vitamin B12 deficiency, iron deficiency, renal failure, alcoholism, hyperbilirubinaemia tends to increase and ongoing haemolysis, hypertriglyceridaemia, chronic liver disease certain drugs tends to reduce HbA1C levels.6

Aforementioned situations are not uncommon in patients with diabetes mellitus and along with haemoglobinopathies we must keep these factors in mind when interpreting Hb1c levels in Indian population.

A large well conducted study by Hardikar et al7 from Pune showed spuriously high prevalence of prediabetes, diagnosed on the basis high HbA1C levels, measured by HPLC techniques, these patients had normal oral glucose tolerance tests. Most of these patients had complete blood counts suggestive of iron deficiency anaemia with low serum ferritin levels. Iron deficiency anaemia is extremely common in India and affects 30-70% of the population depending on which population group from which part of this country one is talking of. In the above mentioned study HbA1C had only 50% sensitivity, 77% specificity and only 20% positive predictive value for the diagnosis of pre diabetes and this falls significantly further when one considers HbA1c levels only in iron deficiency patients.

Unnikrishnan et al has already8 warned about possible interference of haemoglobinopathy in using Hb A1c for diabetes control in Indian population.

In the present discussion we have not evaluated the differences in the biology of endothelial cell health markers, angiogenic genes and HIF and related gene polymorphism which may predispose to differential tendency of developing diabetic retinopathy at similar levels of hyperglycaemia in different population. VEGF also has many polymorphisms and association of diabetic retinopathy with levels of circulating VEGF is now firmly established. Anti VEGF monoclonal antibody Bevaciumab is also successfully used to treat diabetic retinopathy. Moreover many of these VEGF polymorphisms which determines amount of VEGF produced has differential distribution in different
populations. All these suggest that there are many other variables which determine development of retinopathy in diabetes and these variables are variably distributed in different races making racial comparison of HbA1c levels for diabetic retinopathy on a single cut-off value of HbA1c unrealistic.

Preanalytic and analytic variables. Techniques used (measuring more labile Aldimine linked HbA1C along with more stable ketoamine linked HbA1C or only stable Ketoamine product) in measurement of HbA1C may also be important but that is likely to be similar for both Caucasian Asian Indian and black population in US. Hence we have to understand that blood HbA1C level is only a surrogate marker of degree of glycaemic control and its levels associated with prediabetes, diabetes and diabetic retinopathy in different populations may be modulated by many different factors. In India where iron deficiency and haemoglobinopathies are very common we need a separate set of guidelines and levels of HbA1c levels after carefully conducted study to enable us to use this data properly in managing Indian diabetics as there is persuasive reason for not using the HbA1c cut-off used in western literature for Indian population in diagnosing and managing diabetes mellitus.

References