Longitudinal Validation of Hemoglobin A1c Criteria for Diabetes Diagnosis: Risk of Retinopathy

Lucia Sobrin

Receiving a diagnosis of diabetes has significant physical, emotional, and financial consequences (1). The development of precise diagnostic criteria is critical both to avoid the unnecessary burden of treatment in individuals who do not have the disease and to promptly identify individuals who are at risk for developing complications from diabetes so they can be appropriately counseled on disease management.

Traditionally, the diagnosis of diabetes was based on glucose levels associated with the progression to overt, symptomatic disease. In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus refocused the basis of the diagnosis to the relationship between glucose levels and the presence of long-term complications (2). This recommendation was based on the available epidemiological literature demonstrating the association between various glucose measures and microvascular complications of diabetes—particularly retinopathy, which tends to have a stronger correlation to glycemia (2–4). These studies were mainly cross-sectional, although one study did examine microvascular complications longitudinally (4). Most recently, an international expert committee and the American Diabetes Association further specified that diabetes should be diagnosed if hemoglobin A1c is \( \geq 6.5\% \) (5,6). This was based in part on additional studies showing a stronger association between retinopathy and hemoglobin A1c than between retinopathy and fasting plasma glucose (7–9). The specific cut-off point of 6.5% was based on data pooled from nine studies showing that the prevalence of moderate retinopathy begins to rise at a hemoglobin A1c of 6.5% (10).

Previous longitudinal studies of the association of hemoglobin A1c and retinopathy in the general population have not validated this specific cut-off point (Table 1) (4,8,11,12). This can be attributed to limited power with the smaller studies; in addition, in some studies the hemoglobin A1c levels were not analyzed in ranges that permit examining the 6.5% cut-off point specifically. Diagnostic thresholds are ideally informed by incidence data from longitudinal studies. This data translates most directly into what the physician wants to know when faced with a patient with a potential new diagnosis of diabetes: “What are the chances that this patient will develop retinopathy in the future based on the hemoglobin A1c that they have today?” The answer to this question is then weighed against the risks of treatment in deciding whether or not to start therapy.

Tsunagawa et al. (13) present the 3-year incidence of retinopathy in a large Japanese general population cohort with baseline hemoglobin A1c measurements (Table 1). They found that the odds of developing retinopathy at 3 years was 2.35 times greater for participants with a hemoglobin A1c between 6.5 and 6.9% as compared with those with a hemoglobin A1c < 5.0%. This increased risk remained present even after adjusting for other risk factors for retinopathy. The study’s large sample size with both diabetic and nondiabetic patients is a great strength. It provides for sufficient power to detect a diagnostic threshold even after excluding patients who are on treatment for previously diagnosed diabetes; this exclusion removes bias associated with treatment-induced effects on glycemia where the level of glycemia ascertained in the study is likely lower than that which led to retinopathy. The large sample size also allows for fine gradations in the hemoglobin A1c levels examined, increasing the precision of detecting the hemoglobin A1c inflection point at which retinopathy risk increases.

One limitation of the current study is in the definition of retinopathy. Retinopathy with features similar to diabetic retinopathy can be found in nondiabetic populations; risk factors for nondiabetic retinopathy include hypertension (14). In the current study, retinopathy was defined as the presence of hard exudates, cotton wool spots, retinal hemorrhages, or more severe forms of retinopathy. Microaneurysms, which are considered the earliest and most suggestive diagnostic feature of diabetic retinopathy by the widely used Early Treatment Diabetic Retinopathy Study (ETDRS) grading criteria (15), were not part of the definition. Therefore cases with microaneurysms alone, which represent diabetic retinopathy by ETDRS criteria, would not have been classified as having retinopathy in the current study, leading to decreased sensitivity for capturing diabetic retinopathy. Conversely, cases with only retinal hemorrhages or hard exudates are considered as “diabetic retinopathy questionable” by ETDRS criteria. Therefore, the retinopathy definition is also less specific for excluding diabetic retinopathy as classically defined by ETDRS criteria. For the goal of diagnosing diabetes based on a correlation of hemoglobin A1c with diabetic retinopathy, the most sensitive and specific definition of diabetic retinopathy would ideally be used. Although the definition used may have led to misclassification of both case and control subjects, the impact of this is likely small and unlikely to change the outcome of the study. Another limitation of the current work is that it focuses only on Japanese patients and therefore limits generalizability to other populations.

The validation of the current diagnostic threshold for diabetes with longitudinal data lends important support to the diagnostic hemoglobin A1c cut-off point of 6.5%. The data allows physicians to tell their patients with increased...
TABLE 1
Longitudinal studies of the association between hemoglobin A1c and incident diabetic retinopathy

| Author, year       | N     | Hemoglobin A1c (%) categories examined | Hemoglobin A1c cutoff detected for increased risk of incident retinopathy |
|--------------------|-------|---------------------------------------|-------------------------------------------------------------------------|
| McCance et al., 1994 | 927   | <5.4, 5.4–5.7, 5.8–5.9, 6.0–6.1, 6.2–6.3, 6.4–6.6, 6.7–6.8, 6.9–7.3, 7.4–9.0, ≥9.1 | Yes, inflection point at hemoglobin A1c ≥6.9% |
| van Leiden et al., 2003 | 233   | 4.3–5.2, 5.3–5.7, 5.8–13.1             | Yes, participants in highest tertile of hemoglobin A1c had increased risk of incident retinopathy, but this tertile included a large range of hemoglobin A1c values (5.8–13.1%) |
| Selvin et al., 2011   | 767   | <5.7, 5.7–6.5, ≥6.5                    | No, insufficient power to detect cutoff                                 |
| Massin et al., 2011   | 700   | <5.0, 5.0–5.4, 5.5–5.9, 6.0–6.4, 6.5–6.9, ≥7.0 | Yes, inflection point at hemoglobin A1c of 6.0% |
| Tsugawa et al., 2012  | 19,897 | <5.0, 5.0–5.4, 5.5–5.9, 6.0–6.4, 6.5–6.9, ≥7.0 | Yes, inflection point at hemoglobin A1c ≥6.5 |

Confidence that their hemoglobin A1c level above 6.5% puts them at risk for developing the retinal abnormalities of a potentially blinding condition. This provides the patients and physicians with new, more precise data regarding the benefits of initiating diabetes therapy. Additional longitudinal studies of hemoglobin A1c levels and risk of diabetic retinopathy are needed to confirm the findings from Tsugawa et al. and to expand their applicability definitively to other populations.

ACKNOWLEDGMENTS
No potential conflicts of interest relevant to this article were reported.

REFERENCES
1. Schunk M, Reitmeir P, Schipf S, et al. Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany. Diabet Med 2012;29:646–653
2. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
3. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care 1997;20:785–791
4. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994;308:1323–1329
5. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
6. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1):S1–S81
7. Wong TY, Liew G, Tapp RJ, et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 2008;371:736–743
8. van Leiden HA, Dekker JM, Moll AC, et al. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn Study. Arch Ophthalmol 2003;121:245–251
9. Sabanayagam C, Liew G, Tai ES, et al. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? Diabetologia 2009;52:1279–1289
10. Colaguir S, Lee CM, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K, DETECT-2 Collaboration Writing Group. Glyceric thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. Diabetes Care 2011;34:145–150
11. Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Diabetes 2011;60:289–295
12. Massin P, Lange C, Tichet J, et al.; DESIR (Data From an Epidemiological Study on the Insulin Resistance Syndrome) Study Group. Hemoglobin A1c and fasting plasma glucose levels as predictors of retinopathy at 10 years: the French DESIR study. Arch Ophthalmol 2011;129:188–195
13. Tsugawa Y, Takahashi O, Meigs JB, et al. New diabetes diagnostic threshold of hemoglobin A1c and the 3-year incidence of retinopathy. Diabetes 2012;61:3280–3284
14. Wong TY, Klein R, Amirul Islam FM, et al. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study. Am J Ophthalmol 2007;143:970–976
15. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98(Suppl.):786–806