

Longitudinal Validation of Hemoglobin A_{1c} 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 A_{1c} is $\geq 6.5\%$ (5,6). This was based in part on additional studies showing a stronger association between retinopathy and hemoglobin A_{1c} 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 A_{1c} of 6.5% (10).

Previous longitudinal studies of the association of hemoglobin A_{1c} 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 A_{1c} 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 A_{1c} 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.

Tsugawa et al. (13) present the 3-year incidence of retinopathy in a large Japanese general population cohort with baseline hemoglobin A_{1c} measurements (Table 1). They found that the odds of developing retinopathy at 3 years was 2.35 times greater for participants with a hemoglobin A_{1c} between 6.5 and 6.9% as compared with those with a hemoglobin A_{1c} $< 5.0\%$. 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 A_{1c} levels examined, increasing the precision of detecting the hemoglobin A_{1c} 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 A_{1c} 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 A_{1c} cut-off point of 6.5%. The data allows physicians to tell their patients with increased

From the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, and Retina and Uveitis Services, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Corresponding author: Lucia Sobrin, lucia_sobrin@meei.harvard.edu.

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TABLE 1
Longitudinal studies of the association between hemoglobin A_{1c} and incident diabetic retinopathy

Author, year	N	Hemoglobin A _{1c} (%) categories examined	Hemoglobin A _{1c} 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 A _{1c} ≥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 A _{1c} had increased risk of incident retinopathy, but this tertile included a large range of hemoglobin A _{1c} 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 A _{1c} 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 A _{1c} ≥6.5

confidence that their hemoglobin A_{1c} 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 A_{1c} 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.

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