Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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REVIEW

HbA_{1c} for diagnosis of type 2 diabetes. Is there an optimal cut point to assess high risk of diabetes complications, and how well does the 6.5% cutoff perform?

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Abstract: Glycated hemoglobin (HbA_{1c}) has recently been recommended for the diagnosis of type 2 diabetes mellitus (T2DM) by leading diabetes organizations and by the World Health Organization. The most important reason to define T2DM is to identify subjects with high risk of diabetes complications who may benefit from treatment. This review addresses two questions: 1) to assess from existing studies whether there is an optimal HbA_{1c} threshold to predict diabetes complications and 2) to assess how well the recommended 6.5% cutoff of HbA_{1c} predicts diabetes complications. HbA_{1c} cutoffs derived from predominantly cross-sectional studies on retinopathy differ widely from 5.2%–7.8%, and among other reasons, this is due to the heterogeneity of statistical methods and differences in the definition of retinopathy. From the few studies on other microvascular complications, HbA_{1c} thresholds could not be identified. HbA_{1c} cutoffs make less sense for the prediction of cardiovascular events (CVEs) because CVE risks depend on various strong risk factors (eg, hypertension, smoking); subjects with low HbA_{1c} levels but high values of CVE risk factors were shown to be at higher CVE risk than subjects with high HbA_{1c} levels and low values of CVE risk factors. However, the recommended 6.5% threshold distinguishes well between subjects with and subjects without retinopathy, and this distinction is particularly strong in severe retinopathy. Thus, in existing studies, the prevalence of any retinopathy was 2.5 to 4.5 times as high in persons with HbA_{1c}-defined T2DM as in subjects with HbA_{1c} <6.5%. To conclude, from existing studies, a consistent optimal HbA_{1c} threshold for diabetes complications cannot be derived, and the recommended 6.5% threshold has mainly been brought about by convention rather than by having a consistent empirical basis. Nevertheless, the 6.5% threshold is suitable to detect subjects with prevalent retinopathy, which is the most diabetes specific complication. However, most of the studies on associations between HbA_{1c} and microvascular diabetes complications are cross-sectional, and there is a need for longitudinal studies.

Keywords: diabetes mellitus, diagnostic criteria, diagnosis, HbA_{1c}, retinopathy

Introduction

Both the American Diabetes Association (ADA) (2012) and an International Expert Committee (IEC) (2009) recommend a glycated hemoglobin (HbA_{1c}) level of 6.5% as a cutoff for the diagnosis of type 2 diabetes.[1,2] Whereas the IEC considers the HbA_{1c} as a superior criterion for diagnosis of diabetes, the ADA still sees the HbA_{1c} and glucose-based criteria (fasting plasma glucose [FPG] and 2-hour plasma glucose) as equivalent for the diagnosis of diabetes. The World Health Organization (WHO) joined the ADA position and also recommends an HbA_{1c} level ≥6.5% as a diagnostic criterion.[3]

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However, in the WHO report, it was stressed that subjects with HbA_{1c} <6.5% can still be diagnosed with diabetes by glucose-based criteria. As for prediabetes, there is still more disagreement: the members of the IEC are in favor of eliminating the category of prediabetes because the risk of diabetes as measured by the HbA_{1c} is continuous. Nevertheless, the IEC recommends that subjects with an HbA_{1c} in the range of 6.0%–6.4% should be given interventions. The ADA recommends using either HbA_{1c} levels (5.7%–6.4%) or the old FPG (100–125 mg/dL) or the oral glucose tolerance test (140–199 mg/dL) criteria to define prediabetes.

There has been an intensive discussion on benefits and drawbacks of the HbA_{1c} for diagnosing diabetes, which has already been summarized in many reviews.[4–8] An overview of pros and cons of the HbA_{1c} was given by Bonora and Tuomilehto.[4] In brief, there are some obvious advantages of the HbA_{1c}: there is no need to fast, the HbA_{1c} does not reflect acute events like stress or vigorous physical exercise, the preanalytical stability is larger than in glucose measurements, and coefficients of variation are lower than for FPG and oral glucose tolerance test. An important drawback of the HbA_{1c} as a diagnostic criterion is its dependence on various nonglycemic factors.[5] Factors which go together with a decreased turnover of red blood cells, like iron deficiency, renal failure, or vitamin B12 deficiency, lead to higher HbA_{1c} values, whereas factors which coincide with shorter life spans of red blood cells, like hemolytic anemia and chronic liver disease, lead to lower HbA_{1c} levels. Twin studies showed that HbA_{1c} levels also depend on genetic factors.[9] Individual characteristics like hemoglobinopathies (hemoglobin [Hb] S, HbC, HbD), age, and ethnicity also have a strong influence on the HbA_{1c}. Given an identical glucose level, HbA_{1c} levels were shown to increase by 0.4% for the age range of 40–70 years.[10,11] Ethnic differences have been found, for example, in Afro-Americans who have considerably higher HbA_{1c} levels than Whites after adjusting for age, sex, FPG, 2-hour plasma glucose, and other metabolic factors.[12] In a UK multiethnic cohort, South-Asians had a higher HbA_{1c} than White Europeans.[13]

Focus of the present review

Although the HbA_{1c} has been adopted for diabetes diagnosis, there are still various open questions related to the HbA_{1c}-based diagnosis, which have been recently summarized by Sattar and Preiss.[14] These authors were right to point out that there is no gold standard for the definition of diabetes, and that therefore, it is not important to what extent different diagnostic criteria diagnose the same subjects with diabetes. However, perhaps the most important open question is, how well does HbA_{1c} predict complications. This was stated as early as 1994 by McCance et al:[15] "Ultimately such tests can be judged only in terms of their ability to predict a relevant clinical end point, such as the specific complications of diabetes." An identical statement was made in 2009 by the IEC on the role of the HbA_{1c} in the diagnosis of diabetes:[2] "The ultimate goal is to identify individuals at risk for diabetes complications so that they can be treated."

Therefore, the leading questions of this review are the following:

1. Is there an optimal threshold of the HbA_{1c} to predict complications, including retinopathy and other microvascular and macrovascular complications?
2. How well does the recommended HbA_{1c} threshold of 6.5% fulfill the goal of predicting diabetes complications?
3. In view of the strong dependence of the HbA_{1c} on ethnicity, some authors have brought up the issue of ethnic specific cutoffs. Therefore, the question is, are there ethnic differences in associations of HbA_{1c} levels with diabetes complications?

Sattar and Preiss stated that to judge the ability of diagnostic criteria to predict complications, the focus should be on microvascular complications, not on macrovascular complications.[14] They argued that newly diagnosed diabetes has now been shown not to be a full equivalent of a former myocardial infarction as previously believed, and that patients with diabetes benefit so strongly from medication, that cardiovascular risk can be brought down below 20%. All the same, macrovascular complications will be taken into account in this review because in persons with diabetes, the burden of disease caused by macrovascular complications is much larger than that of microvascular complications.

Methods

To identify literature addressing the associations between HbA_{1c} and microvascular complications, several strategies were used for this narrative review. In the PubMed database, the following terms were combined as medical subject headings or text words: "HbA_{1c}" and (threshold or cutoff or cut point) and (microvascular complications or retinopathy or neuropathy or nephropathy or albuminuria). Moreover, an overview published by the WHO in 2010 was used.[16] Cross-sectional and longitudinal studies were included. For literature identified, we checked the Web of Knowledge citation index for other papers which had cited this literature. Literature on the associations between HbA_{1c} and macrovascular

complications was identified in a similar manner, and two recent meta-analyses were taken into account.[17,18]

Is there an optimal threshold of the HbA_{1c} for microvascular complications?

Retinopathy

Ideally, thresholds of HbA_{1c} for retinopathy are determined in a way that subjects with HbA_{1c} levels above the threshold have a much larger probability of having or developing retinopathy, and subjects with HbA_{1c} levels below the threshold have a much lower probability of having or getting this microvascular complication. Table 1 shows characteristics and main findings of studies done to identify thresholds of HbA_{1c} for retinopathy. Cutoffs range widely from 5.2%–7.8%. In some studies, like the Atherosclerosis Risk In Communities (ARIC) Study, no threshold could be identified.[19] In a further cross-sectional study carried out in Malay people, no threshold was found when change-point models were used for detection of a cutoff.[20] In addition, areas under the receiver operating curve (AROCs) were reported for a few studies. These AROCs can be seen as a measure of how strongly HbA_{1c} is related to the prevalence or incidence of retinopathy. Most AROCs reported for the association between HbA_{1c} and prevalent or incident retinopathy are in the range of 0.7–0.8 which can be interpreted as moderate to fairly good. However, in the ARIC and in the Data from an Epidemiological study on the Insulin Resistance syndrome (DESIR) study, lower AROCs were found.[19,21] The sum of these studies suggests that HbA_{1c} is associated with prevalent retinopathy, but there is no evidence of a consistent threshold.

Contrary to this conclusion, the recommendations of the IEC to diagnose diabetes by a cutoff of the HbA_{1c} of 6.5% were based on the assumption that there is a sharp and consistent threshold.[2] In the IEC report, much importance was attached to recent findings of the Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) study.[22] In DETECT-2, data from nine studies and five countries were pooled, and the number of participants was 44,623. For HbA_{1c}, a low prevalence of retinopathy was seen until the 17th vigintile, which was followed by a sharp increase. From vigintiles of HbA_{1c}, a threshold range of 6.3%–6.7% was derived; from continuous levels of HbA_{1c}, a similar threshold range of 6.5%–6.9% was identified. Finally, a cut point of 6.4% was seen as optimal in receiver operating characteristic curve analysis. It was mainly from these DETECT-2 findings that the IEC recommended a cutoff of 6.5% for the HbA_{1c}-based diagnosis of diabetes. Moreover, the IEC referred to three epidemiological studies done in the 1990s. This is the study on Pima Indians, on Egyptians, and on US subjects participating in the National Health and Nutrition Examination Survey (NHANES) study.[15,23,24] For each of these three studies, prevalence of retinopathy was shown by deciles of HbA_{1c}, and fairly sharp inflection points were seen by visual inspection.

Ideally, to look for associations between measures of glycemia and long-term complications, longitudinal studies with subjects free of diabetes and free of retinopathy at baseline should be carried out. However, DETECT-2 is a cross-sectional study, and subjects with known diabetes were not excluded, and this applies also to the other three studies mentioned above. Actually, most of the studies presented in Table 1 are cross-sectional studies. So far, there are only three longitudinal studies looking at the association between HbA_{1c} and retinopathy. However, in the Hoorn study, the number of participants was so low that no threshold was reported.[25] In a recent study on Japanese subjects, follow-up was 3 years, and a threshold range of 6.5%–6.9% was calculated.[26] In the DESIR study, the follow-up was 10 years, and a threshold of 6.0% was derived.[21]

There are several reasons why thresholds of HbA_{1c} for retinopathy differ so widely in the studies done so far. First, there is a considerable variation in (statistical) methods of determining the cutoffs from HbA_{1c} data and prevalence or incidence data of retinopathy. As can be seen from Table 1, the most often used methods are visual inspection; calculation of the cutoff, which belongs to the maximum Youden index (the Youden index is the sum of sensitivity and specificity minus 1); change-point models; and logistic regression analyses. Interestingly, thresholds varied strongly even for the same data when different methods were applied. To give an example, in the Australian Diabetes, Obesity and Lifestyle study, the cutoff was 6.1% by visual inspection.[27] When change-point models were used, results strongly depended on model adjustment. Without any adjustment, a threshold of 5.2% was calculated; with adjustment for age, sex, and blood pressure, the threshold was 5.6%, and after a more comprehensive adjustment, the cutoff was 6.0%. In the DETECT-2 study, and the studies on Pima Indians and Egyptians, unadjusted analyses were done.[15,22,23]

Second, results depend widely on the definition of retinopathy. In the NHANES study, and the two studies on Pima Indians and Egyptians, strong associations between FPG and retinopathy had been reported with a sharp FPG

Table 1 Studies on the identification of HbA_{1c} thresholds for prevalent or incident retinopathy

Study	Study population characteristics	Definition of retinopathy	Method/criterion of determining cutoff	Cutoff	AROC	Sensitivity	Specificity	Cases of retinopathy above/below cutoff
McCance et al[15]	Cross-sectional; 960 Pima Indians; age ≥25 years; exclusion of subjects receiving insulin or oral hypoglycemic treatment at the last examination	At least one microaneurysm or hemorrhage or proliferative retinopathy	Crossing point of the two components of a bimodal HbA_{1c} distribution	7.8%	–	65.6	87.6	15.6%/1.3%
			Equivalent to 2hPG cutoff of 11.1 mmol/L	6.1%	–	81.3	76.8	NR
			Maximum of Youden index	7.0%	NR	78.1	84.7	NR
McCance et al[15]	Longitudinal; 960 Pima Indians; age ≥25 years; subjects receiving insulin or oral hypoglycemic treatment at baseline were excluded; assessment of incidence of retinopathy after 5 years	At least one microaneurysm or hemorrhage or proliferative retinopathy	Crossing point of the two components of a bimodal HbA_{1c} distribution	7.8%[a]	–	–	–	Incident cases above/below cutoff: 22.9%/1.1%
Engelgau et al[23]	Cross-sectional; 1,018 Egyptians; age ≥20 years; subjects with diabetes not excluded	Bilateral retinal fundus photography	Increase between 7th and 8th decile (entire population)	6.9%	–	78%	78%	28%/5%
			Increase between 9th and 10th decile (excluding subjects with antihyperglycemic medication)	7.5%		NR	NR	18%/5.6%
Expert committee; NHANES III[24]	Cross-sectional; n=2,821; age 40–74 years	Fundus photography	Increase between 9th and 10th decile	6.2%	–	NR	NR	NR
Ito et al[43]	Cross-sectional; 12,208 Japanese exposed to atomic bomb radiation in 1945; age 16–99 years; no exclusion of subjects with known diabetes	Bilateral fundus photography	Test of significant changes in prevalence of retinopathy between subsequent deciles	7.3%	–	NR	NR	4.2%/1.0%[b]
van Leiden et al; Hoorn study[25]	Longitudinal; follow-up 7.9–11.0 years; n=233; age 50–74 years; analyses in total study group and in subjects without diabetes	Presence of at least one microaneurysm, hemorrhage, or hard exudate	Logistic model with categories of HbA_{1c} (adjusted for age, sex, hypertension, glucose metabolism category)	Increase in incidence of retinopathy for HbA_{1c} in the range of 5.8%–13.1% compared to HbA_{1c} 4.3%–5.2%; no threshold reported				
Miyazaki et al; Hisayama study[44]	Cross-sectional; 1,637 Japanese; age 40–79 years; no exclusion of subjects with known diabetes	Fundus examination with grading by Airlie House classification	Maximum of Youden index	5.7%	0.945	86.5	90.1	20%/2%

(*Continued*)

Table 1 (*Continued*)

Study	Study population characteristics	Definition of retinopathy	Method/criterion of determining cutoff	Cutoff	AROC	Sensitivity	Specificity	Cases of retinopathy above/below cutoff
Tapp et al; AusDiab study[27]	Cross-sectional; n=2,182; age ≥25 years; no exclusion of subjects with known diabetes	Presence of at least one definite retinal hemorrhage and/or microaneurysm	Visual (total population)	6.1%	–	NR	NR	21.3%/6.6%
			Visual (exclusion of subjects on hypoglycemic medication)	No threshold found				
			Change-point model without adjustment	5.2%	–	NR	NR	NR
			Change-point model adjusted for age, sex, blood pressure	5.6%	–	NR	NR	NR
			Change-point model with further adjustment for diabetes duration	6.0%	–	NR	NR	NR
Sabanayagam et al[20]	Cross-sectional; 3,190 Malay people; age 40–80 years; subjects with diabetes not excluded	Two digital fundus photographs; retinopathy was defined by ETDRS scores (any ≥15; mild ≥20; moderate >43)	Maximization of Youden index for any retinopathy	7.0%	0.754	55.6	85.0	35.4%/7.2%
			Maximization of Youden index for mild retinopathy	6.6%	0.899	87.0	77.1	NR
			Maximization of Youden index for moderate retinopathy	7.0%	0.904	82.9	82.3	15.8%/0.8%
			Change-point model for any retinopathy	No threshold observed				
			Change-point model for mild retinopathy	No threshold observed				
			Change-point model for moderate retinopathy	No threshold observed				
Cheng et al; NHANES study[45]	Cross-sectional; 1,066 Americans; age ≥40 years	Two 45° nonmydriatic photographs; retinopathy was defined as a score ≥14 by ETDRS severity scale	Joinpoint regression: deciles	5.5%	0.71	80	37	12.7% increase in prevalence of retinopathy above cutoff/0.7% increase below cutoff per 1% increment of HbA_{1c}
			Joinpoint regression: Pima cutpoints	5.5%				
			Joinpoint regression: 0.1 increments of HbA_{1c}	5.5%				
			Joinpoint regression after exclusion of subjects on hypoglycemic medication	5.5%	–	–	–	10.5% increase in prevalence of retinopathy above cutoff/0.8% increase below cutoff per 1% increment of HbA_{1c}

(*Continued*)

Table 1 (*Continued*)

Study	Study population characteristics	Definition of retinopathy	Method/criterion of determining cutoff	Cutoff	AROC	Sensitivity	Specificity	Cases of retinopathy above/below cutoff
Massin et al; DESIR study[21]	Longitudinal; 10 year follow-up; n=700; one group of 235 subjects with diabetes, and two age, sex, and study center matched groups (n=227 and n=238, respectively), with FPG level 110–125 mg/dL, and FPG <110 mg/dL, respectively; age 30–65 years	Subjects with microaneurysms, hemorrhages, exudates, cotton-wool spots, intramicrovascular abnormalities, venous bleeding, or new vessels	Increase in positive predictive value[c]	6.0%	0.64	19%	92%	NR
Selvin et al; ARIC study[19]	Cross-sectional; 10,584 subjects without known diabetes	Nonmydriatic 45° retinal photograph; retinopathy was defined by ETDRS scores (none <14, mild 14–20, moderate to severe ≥35)	Cubic-spline models with maximization of likelihood ratio with respect to location of threshold	No evidence for presence of a threshold (AROC for any retinopathy: 0.561 AROC for mild retinopathy: 0.543 AROC for moderate to severe retinopathy: 0.658)				
Colagiuri et al; DETECT-2 collaboration[22]	Cross-sectional; pooled analysis of nine studies from five countries; n=44,623; age 20–79 years; subjects with known diabetes (13.8%) not excluded	Use of gradable retinal photographs; different methods of classifying and assessing retinopathy between studies	Maximum of Youden index	6.4%	–	84.5	87.0	–
			Logistic regression adjusted for study center (applied to continuous distribution)	6.5%–6.9%	–	80.1[d]	89.7[d]	–
			Logistic regression adjusted for study center (applied to vigintile distribution)	6.3%–6.7%	–	82.8[d]	88.1[d]	–
Xin et al[30]	Cross-sectional; 2,551 Chinese; age 18–79 years; FPG ≥5.6 mmol/L; no exclusion of subjects with known diabetes	Bilateral retinal fundus photography	Maximization of Youden index (total sample)	6.8%	0.864	85.1	88.0	NR
			Maximization of Youden index (exclusion of subjects receiving antihyperglycemic medication)	6.9%	0.725	60.7	93.6	
			Joinpoint regression (total sample)	6.4%	–	85.1	82.1	NR
			Joinpoint regression (exclusion of subjects receiving antihyperglycemic medication)	6.7%	–	60.7	91.6	

(*Continued*)

Table 1 (*Continued*)

Study	Study population characteristics	Definition of retinopathy	Method/criterion of determining cutoff	Cutoff	AROC	Sensitivity	Specificity	Cases of retinopathy above/below cutoff
Tsugawa et al[36]	Cross-sectional; 2,804 White and 1,008 Black Americans; analysis of whole study group and of subjects not treated for diabetes only; age ≥40 years	One or more microaneurysms or more severe forms of retinopathy; Airlie House classification	Visual inspection of cubic-spline models	Cutoff "near 5.5%" in Blacks, "at higher HbA_{1c} levels" in Whites				
Tsugawa et al[26]	Cross-sectional; 20,433 Japanese subjects; age ≥21 years; subjects with known diabetes not excluded	Presence of hard exudates, cotton wool spots, retinal hemorrhage, or more severe forms of retinopathy; Fukuda standard A2 or higher	Test for nonlinearity in multivariate logistic regression models with restricted cubic spline	No threshold found for prevalence of retinopathy (test for nonlinearity: P=0.08)				
Tsugawa et al[26]	Longitudinal; 3 years follow-up; 19,987 Japanese subjects; age ≥21 years; subjects with known diabetes not excluded	Presence of hard exudates, cotton wool spots, retinal hemorrhage, or more severe forms of retinopathy; Fukuda standard A2 or higher	Test for nonlinearity in multivariate logistic regression models with restricted cubic spline	"Possible threshold at HbA_{1c} levels between 6.0 and 7.0" (test for nonlinearity: P=0.001)				
			Multivariate logistic regression with categories of HbA_{1c} as independent variable	6.5%–6.9%	–	–	–	–
Cho et al[29]	Cross-sectional; 3,403 participants from South Korea; age 40–69 years; 24% of the subjects had diabetes by ADA criteria	Single-field nonmydriatic fundus photography	Maximization of Youden index: any retinopathy	6.6%	0.83	76.2	84.2	8.4%/0.5%
			Maximization of Youden index: moderate/severe retinopathy	6.9%	0.84	77.1	88.7	6.6%/0.3%
			Logistic regression (unadjusted): any retinopathy	6.9%	–	68.3	89.0	10.5%/0.7%
			Logistic regression (unadjusted): moderate/severe retinopathy	6.9%	–	77.1	88.7	6.6%/0.3%
			Logistic regression (multivariable adjustment): any retinopathy	6.9%	–	68.3	89.0	10.5%/0.7%
			Logistic regression (multivariable adjustment): moderate/severe retinopathy	6.9%	–	77.1	88.7	6.6%/0.3%

Notes: [a]The value "9.4%" indicated in Table 2 of the paper by McCance et al (1994) is obviously a mistake. [b]Prevalence of retinopathy below threshold was calculated by the authors. [c]Visual inspection of the frequency of retinopathy according to baseline HbA_{1c} would lead to a much larger cutoff but was not assessed by the authors. [d]Values were calculated for the middle of the range.

Abbreviations: 2hPG, 2-hour plasma glucose; ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; AROC, area under the receiver operating characteristic curve; AusDiab, Australian Diabetes Obesity and Lifestyle study; DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; DETECT-2, Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance; ETDRS: Early Treatment Diabetic Retinopathy Study; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey; NR, not reported.

cutoff of 7.0 mmol/L.[15,23,24] However, as pointed out by Wong et al, a direct clinical ophthalmoscopic examination was done in the Pima Indian study, and only one retinal photograph was taken in the two other studies.[28] When multiple retinal photographs of each eye were used to diagnose retinopathy, the association between FPG and retinopathy was much weaker as indicated by AROCs between 0.56–0.61, and no sharp threshold could be observed anymore.

Accordingly, thresholds of HbA_{1c} for retinopathy may also depend on the method used to diagnose retinopathy. Furthermore, mild retinopathy can also occur in persons without diabetes, and thresholds for mild retinopathy can differ from thresholds for moderate retinopathy. In a South Korean study, for example, the cutoff derived from AROCs was 6.6% for any retinopathy, and 6.9% for moderate or severe retinopathy.[29] In Malay people, thresholds of 6.6% and 7.0%, respectively, were calculated from receiver operating characteristic curves for mild and moderate retinopathy.[20] The methods sections of some papers suggest that studies differ in the definition of what is a mild or moderate retinopathy. To give an example, in the ARIC study and in the Malay study, grades of retinopathy were defined according to a modification of the so-called Arlie House classification system, which had been used in the Early Treatment Diabetic Retinopathy study (ETDRS).[19,20] In ARIC, mild retinopathy was defined as ETDRS 14–20, where as ETDRS >20 (and ≤ 43) was used as a criterion for mild retinopathy in the Malay study.

Third, thresholds of HbA_{1c} for retinopathy depend on the choice of exclusion criteria. In a Chinese study, for example, a cutoff of 6.4% was determined for the whole study group when a nonlinear regression model was used.[30] After exclusion of subjects receiving antihyperglycemic medication, the cutoff was 6.7% with use of the same method.

Fourth, HbA_{1c} distributions may not be the same for different ethnicities, and a shift of HbA_{1c} distributions to the left or to the right would influence the position of the threshold. The question of ethnicity-specific cutoffs will be discussed in more detail below.

Fifth, thresholds were identified from deciles of HbA_{1c} in many studies. Thus, the choice of cutoffs depends strongly on the position of deciles, and thus on the distribution of HbA_{1c}. Particularly in smaller study groups, the precise position of deciles may to some extent depend on chance.

Sixth, discrepancies in threshold assessment might be due to differences in the measurement of HbA_{1c}, in particular in older studies which were carried out when the standardization of HbA_{1c} measurements was less advanced.

Other microvascular complications

Meanwhile, there are a lot of studies on thresholds for retinopathy, but as can be seen from Table 2, there are fewer studies on thresholds for other microvascular complications.

As indicated by AROCs, associations between HbA_{1c} and prevalent/incident microvascular complications other than retinopathy are quite poor. So far, AROCs have been reported in the ARIC study and in the Malay study, and range from 0.56–0.67.[19,20] Moreover, in most studies, no thresholds were reported. In the Malay study, cutoffs of HbA_{1c} for chronic kidney disease (6.6%), microalbuminuria or macroalbuminuria (7.0%) and peripheral neuropathy (6.6%) were obtained from maximizing the Youden index.[20] However, maximizing the Youden index and reporting the corresponding cutoff is always possible. The sums of sensitivity and specificity calculated for these cutoffs in the Malay study are in the range of 1.1–1.2, which is again quite poor – remember that a figure of 1 for the sum of sensitivity and specificity corresponds to the minimum of information possible. For the cutoffs calculated for retinopathy, the sums of sensitivity and specificity were in the range of 1.5–1.6 in most studies, and thus demonstrated that cutoffs of HbA_{1c} were much sharper in retinopathy than in other microvascular complications. When change-point modeling was used in the Malay study, no thresholds of HbA_{1c} for microvascular complications other than retinopathy could be found anymore.[20] In the Australian Diabetes, Obesity and Lifestyle study, a cutoff of HbA_{1c} was found for microalbuminuria by visual inspection.[27] However, change-point modeling gave no evidence for a threshold anymore.

The studies shown in Table 2 are all cross-sectional, and subjects with known diabetes were not excluded. The only exception is the ARIC study, which is longitudinal with a long follow-up and an analysis stratified for participants with and without diabetes.[19] In this study, it became particularly evident that there is no threshold of HbA_{1c} for chronic kidney disease and end-stage renal disease, respectively.

Macrovascular complications

In several meta-analyses, associations between glycemic measures and cardiovascular diseases have been found in ranges of glycemia usually seen as nondiabetic.[17,18,31] To give an example, an HbA_{1c} level of 5% is far below the cut points recommended for the diagnosis of prediabetes or diabetes. Nevertheless, as shown in more detail below, the risk of CVE has been shown to be larger for subjects with an HbA_{1c} level of 5% compared to subjects with an HbA_{1c} level of 4.27%.[17] This is not surprising because increased cardiovascular risk

Table 2 Studies on the identification of HbA_{1c} thresholds for prevalence or incidence of microvascular complications (except retinopathy)

Study	Study characteristics	Microvascular complication	Method of determining cutoff	Cutoff	Sensitivity	Specificity	Cases above/below cutoff	AROC
McCance et al[15]	Cross-sectional; 960 Pima Indians; age ≥25 years; exclusion of subjects receiving insulin or oral hypoglycemic treatment at the last examination	Nephropathy	Crossing point of the two components of a bimodal HbA_{1c} distribution	7.8%	40.0	86.6	7.5%/1.8%	–
	Longitudinal; 960 Pima Indians; age ≥25 years; subjects receiving insulin or oral hypoglycemic treatment at baseline were excluded; assessment of incidence of retinopathy after 5 years	Nephropathy	Crossing point of the two components of a bimodal HbA_{1c} distribution	7.8%[a]	–	–	3.8%/1.4%	–
Tapp et al; AusDiab[27]	Cross-sectional; n=2,389; age ≥25 years; no exclusion of subjects with known diabetes	Microalbuminuria	Visual inspection Change-point model	6.1% No significant threshold	NR	NR	29.8%/11.2%	–
Sabanayagam et al[20]	Cross-sectional; 3,190 Malay people; age 40–80 years; subjects with diabetes not excluded	Chronic kidney disease	Maximum of Youden index	6.6%	37.9	76.6	–	0.615
		Microalbuminuria or macroalbuminuria	Maximum of Youden index	7.0%	31.8	90.6	–	0.673
		Peripheral neuropathy	Maximum of Youden index	6.6%	66.5	41.5	–	0.573
		Chronic kidney disease	Change-point model	No threshold observed			–	–
		Microalbuminuria or macroalbuminuria	Change-point model	No threshold observed			–	–
		Peripheral neuropathy	Change-point model	No threshold observed			–	–
Selvin et al; ARIC study[19]	Longitudinal; median of follow-up 14 years; 10,584 subjects without diabetes at baseline	Chronic kidney disease	Maximum likelihood ratio method	No evidence for a threshold (*P*-values for presence of a threshold: *P*=0.54 (adjustment for age, sex, and race; *P*=0.59 [multivariable adjustment])				0.562
Bongaerts et al; KORA F4 study[46]	Cross-sectional; n=1,100; age 61–82 years; no exclusion of subjects with known diabetes	Distal sensorimotor polyneuropathy (DSPN)	Logistic regression with categories of HbA_{1c}	No relationship between quartiles of HbA_{1c} and DSPN				
Hernandez et al[47]	Cross-sectional; n=2,270; age 18–80 years; no exclusion of subjects with known diabetes	Combined endpoint of chronic kidney disease or cardiovascular disease	Maximum of Youden index	5.5%	82	55	–	0.76

Note: [a]The figure "9.4%" indicated in Table 2 of the paper by McCance (1994) is obviously a mistake.

Abbreviations: HbA1c, glycated hemoglobin; ARIC, Atherosclerosis Risk in Communities; AROC, area under the receiver operating characteristic curve; AusDiab, Australian Diabetes Obesity and Lifestyle study; KORA, Cooperative Health Research in the Region of Augsburg; NR, not reported.

has not been used as a criterion for the selection of cutoffs of glycemic measures.

In two older reviews, continuous relationships were reported between glucose levels and CVE which started in the nondiabetic range and continued in the diabetic range.[32,33] Although the studies presented in these reviews were based on measurements of fasting glucose, 1- and 2-hour glucose, and random glucose, the conclusions drawn in these reviews might be relevant for the question of relationships between glycemic measures (including HbA_{1c}) and CVE in general. Coutinho et al stated that it is difficult to tell from an exponential curve whether it is continuous or whether there is a threshold, and moreover, that a threshold might be even below the prediabetic range if there were a threshold at all.[32]

A more recent meta-analysis covered seven prospective studies which included nine datasets with cardiovascular disease (CVD) as the outcome, and seven datasets with cardiovascular death as the outcome.[17] As a result, the risk of CVE was increased even in slightly higher HbA_{1c} levels. With an HbA_{1c} level of 4.27% as a reference, the risk of CVE was 13% higher for an HbA_{1c} level of 5%, 34% higher for an HbA_{1c} level of 6%, and 58% higher for an HbA_{1c} level of 7%. From the meta-analysis, an exponential relationship was derived between HbA_{1c} and cardiovascular death which did not suggest the existence of a threshold. In a further recent meta-analysis of nine prospective studies on the association of HbA_{1c} with coronary heart disease (CHD), a significant overall association in the nondiabetic range was found (hazard ratio [HR] =1.20, 95% confidence interval [CI] 1.10–1.31); however, a threshold was not reported in this meta-analysis.[18]

Results from the ARIC study on the relationship between HbA_{1c} and cardiovascular risk in 11,092 Black and White US adults, with a median follow-up of 14 years, were not included in the two meta-analyses.[34] After multivariable adjustment, a clear trend was found between categories of HbA_{1c} and CHD ($P<0.001$) and HbA_{1c} and ischemic stroke ($P<0.001$). With HbA_{1c} 5.0 to <5.5% as the reference, the CHD risk increased by 23% for HbA_{1c} 5.5 to <6.0%, by 78% for 6.0 to <6.5%, and by 95% for HbA_{1c} ≥6.5%. The authors assumed that there was "a possible threshold" of HbA_{1c} for CHD risk: for HbA_{1c} <5.0% as the reference, a HR of 1.38 (95% CI 1.22–1.56) per 1% of HbA_{1c} was reported for HbA_{1c} levels above 5.5%.

To conclude, there is strong evidence of a continuous association between HbA_{1c} and CVD. Some authors discuss a threshold of HbA_{1c} for CVD far below the diabetic threshold, but there is little evidence that this could be a sharp cutoff.

How well does the recommended HbA_{1c} threshold of 6.5% fulfill the goal of predicting diabetes complications?

As shown above, no distinct and consistent threshold of HbA_{1c} was found for retinopathy. For other microvascular complications and for macrovascular complications no convincing evidence has been presented for the existence of a threshold.

In view of the many methodical problems which come up upon selecting a threshold, even for retinopathy, we would suggest a more pragmatic decision. The recommended HbA_{1c} threshold of 6.5% is acceptable if the frequency of prevalent/incident complications is considerably higher in subjects with HbA_{1c}-defined diabetes than in subjects with a lower HbA_{1c}.

In several cross-sectional studies, the prevalence of any retinopathy was considerably higher for HbA_{1c} ≥6.5% than for HbA_{1c} <6.5% (Tables 3 and 4). In the Reykjavik study, the Malay study, and the NHANES study (Whites), respectively, prevalence of any retinopathy was 2.5, 4.5, and 3.0 times as high in persons with HbA_{1c}-defined diabetes as in subjects with HbA_{1c} levels below the threshold.[20,35,36] In the ARIC study, however, subjects with HbA_{1c} ≥6.5% did not have larger odds of any retinopathy (HR =0.91, 95% CI 0.54–1.54) than subjects with HbA_{1c} <5.7% after multivariable adjustment.[19] When these analyses were confined to more severe grades of retinopathy, the 6.5% threshold distinguishes much better between subjects with and without prevalent retinopathy. In the Reykjavik study, the prevalence of moderate retinopathy was 2.5% for HbA_{1c} ≥6.5%, but only 0.1% for lower HbA_{1c} levels.[35] In the Malay study, the prevalence of moderate retinopathy was about 30 times higher in HbA_{1c} ≥6.5% than in HbA_{1c} <6.5%.[20] In the ARIC study, the odds of moderate/severe retinopathy was 2.9 (95% CI 1.2–7.1) times higher in HbA_{1c} ≥6.5% than in HbA_{1c} <6.5%.[19]

However, the 6.5% threshold distinguishes less well between persons with and without microvascular complications other than retinopathy. In the Malay study, for example, the prevalence of chronic kidney disease was 29.9% in subjects with HbA_{1c} ≥6.5% and 17.8% in subjects with lower HbA_{1c} levels.[20] For prevalence of microalbuminuria and macroalbuminuria, the corresponding figures were 58.9% and 29.6%, respectively; and for prevalence of

Table 3 Association of HbA_{1c} based diagnosis of type 2 diabetes (HbA_{1c} ≥6.5%) with prevalence or incidence of microvascular complications

Study	Study characteristics	Microvascular complication considered	Prevalence of microvascular complications	
			HbA_{1c} ≥6.5%	HbA_{1c} <6.5%
Sabanayagam et al[20]	Cross-sectional study in Malay people; age 40–80 years; subjects with diabetes not excluded; n=3,190 (chronic kidney disease) n=930 (microalbuminuria and macroalbuminuria) n=855 (peripheral neuropathy)	Prevalence of any retinopathy	28.6%	6.4%
		Prevalence of mild retinopathy	17.2%	0.8%
		Prevalence of moderate retinopathy	12.2%	0.4%
		Prevalence of chronic kidney disease	29.9%	17.8%
		Prevalence of microalbuminuria and macroalbuminuria	58.9%	29.6%
		Prevalence of peripheral neuropathy	23.9%	16.7%
Tsugawa et al[36]	Cross-sectional; 2,527 White and 805 Black Americans; age ≥40 years	Prevalence of retinopathy (subjects not treated for T2DM, Whites only)	12.3% (95% CI 4.5–20.1)	4.1%[a]
		Prevalence of retinopathy (subjects not treated for T2DM, Blacks only)	17.1% (95% CI 6.9–27.2)	6.7%[a]
Gunnslaugsdottir; Reykjavik study (AGES-R)[35]	Cross-sectional; n=4,994; age ≥67 years	Prevalence of any retinopathy	27.0% (95% CI 23.2–31.0)	10.7% (95% CI 9.8–11.6)
		Prevalence of mild retinopathy	23.4% (95% CI 19.8–27.4)	10.6% (95% CI 9.7–11.5)
		Prevalence of moderate retinopathy	2.5% (95% CI 1.4–4.3)	0.1% (95% CI 0.0–0.2)
		Prevalence of proliferative diabetic retinopathy	1.0% (95% CI 0.3–2.3)	0

Note: [a]Prevalence of retinopathy below threshold was calculated by the authors.
Abbreviations: HbA1c, glycated hemoglobin; AGES-R, the Age, Gene/Environment Susceptibility – Reyjkavik Study; CI, confidence interval; T2DM, type 2 diabetes mellitus.

peripheral neuropathy, these figures were 23.9% and 16.7%, respectively.

For cardiovascular outcomes, establishing an HbA_{1c} threshold makes less sense than for microvascular complications because CVD risk depends on many strong risk factors, including HbA_{1c}. This was demonstrated in the European Prospective Investigation of Cancer Norfolk study for 10,144 men and women free of diabetes at baseline.[37] With adjustment for age only, the relative risk of CVD was 1.31 (95% CI 1.13–1.52) in HbA_{1c} 5.5%–5.9%, 1.50 (95% CI 1.22–1.84) in HbA_{1c} 6.0%–6.4%, 2.19 (95% CI 1.55–3.09) in HbA_{1c} 6.5%–6.9%, and 3.21 (95% CI 2.50–4.13) in HbA_{1c} ≥7.0% (reference HbA_{1c} <5.5%). However, participants with a low level of HbA_{1c}, but raised values of other CVD risk factors (eg, systolic blood pressure, ratio of total cholesterol to HDL cholesterol, smoking) had a much higher risk of CVD than participants with a high HbA_{1c} level and lower values of the other CVD risk factors.

Studies on CVD prediction models confirm that glycemic measures are of minor importance for the assessment of CVD risk. In the Framingham Offspring study, the AROC of the sex-adjusted Framingham Risk score for the prediction of CVD was 0.744.[38] When HbA_{1c} was added to this prediction model, the AROC was 0.740, ie, there was no improvement of CVD prediction at all. This finding confirms that prediction of macrovascular complications should only play a marginal role with regard to HbA_{1c} thresholds for diabetes. The idea that the HbA_{1c} should be combined with other risk factors in preventive interventions was demonstrated in the Anglo-Danish-Dutch study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study.[39] Subjects who might benefit from interventions were defined by either screen detected diabetes or by excess mortality. HbA_{1c} alone identified only 20% of those who might benefit from lifestyle intervention or medical treatment, whereas a combination of HbA_{1c} ≥6.0% and an elevated cardiovascular risk, defined by the Systematic COronary Risk Evaluation (SCORE) of ≥ 5, identified 96.7% of these subjects.

In the Danish part of the ADDITION study, it was demonstrated that the 6.5% threshold of HbA_{1c} is useful to predict mortality in subjects with normal glucose tolerance.[40] After multivariable adjustment, the risk of all-cause mortality was significantly increased for HbA_{1c} ≥6.5% (HR =2.48, 95% CI 1.23–4.99) compared to HbA_{1c} <6.0%. Thus, in this Danish study group, normal glucose tolerance subjects with HbA_{1c} ≥6.5% had a similar risk of all-cause mortality as subjects with known type 2 diabetes. However, a limitation

Table 4 Association of HbA_{1c} based diagnosis of type 2 diabetes and prediabetes (HbA_{1c} ≥6.5%, and HbA_{1c} 5.7% to <6.5%, respectively) with prevalence or incidence of microvascular complications

Study	Study characteristics	Microcomplication considered	Adjusted ORs (95% CI) and HRs (95% CI), respectively		
			HbA_{1c} <5.7%	HbA_{1c} 5.7 to <6.5%	HbA_{1c} ≥6.5%
Selvin et al; ARIC study[19]	Cross-sectional; 10,584 subjects without known diabetes	Prevalence of any retinopathy (adjusted for age, sex, and race)	OR =1	0.98 (0.73–1.33)	1.25 (0.75–2.07)
		Prevalence of any retinopathy (multivariable adjustment)	OR =1	0.84 (0.61–1.14)	0.91 (0.54–1.54)
		Prevalence of mild retinopathy (adjusted for age, sex, and race)	OR =1	0.88 (0.62–1.23)	0.85 (0.45–1.60)
		Prevalence of mild retinopathy (multivariable adjustment)	OR =1	0.77 (0.54–1.08)	0.65 (0.34–1.23)
		Prevalence of moderate/severe retinopathy (adjusted for age, sex, and race)	OR =1	1.76 (0.87–3.57)	4.35 (1.83–10.31)
		Prevalence of moderate/severe retinopathy (multivariable adjustment)	OR =1	1.42 (0.69–2.92)	2.91 (1.19–7.11)
	Longitudinal; median of follow-up 14 years; 10,584 subjects without diabetes at baseline	Incidence of chronic kidney disease (adjusted for age, sex, and race)	HR =1	1.31 (1.10–1.55)	1.84 (1.39–2.43)
		Incidence of chronic kidney disease (multivariable adjustment)	HR =1	1.12 (0.94–1.34)	1.39 (1.04–1.85)
		Incidence of ESRD (adjusted for age, sex, and race)	HR =1	2.00 (1.10–3.61)	3.04 (1.31–7.09)
		Incidence of ESRD (multivariable adjustment)	HR =1	1.51 (0.82–2.76)	1.98 (0.83–4.73)
Bower et al; NHANES[41]	Cross-sectional; 2,612 non-Hispanic Whites without history of diabetes	Prevalence of retinopathy (adjusted for age and sex)	OR =1	1.30 (0.89–1.90)	1.22 (0.47–3.16)
		Prevalence of retinopathy (multivariable adjustment)	OR =1	1.23 (0.84–1.80)	1.16 (0.40–3.32)
	Cross-sectional; 805 non-Hispanic Blacks without history of diabetes	Prevalence of retinopathy (adjusted for age and sex)	OR =1	1.45 (0.78–2.73)	2.71 (1.06–6.93)
		Prevalence of retinopathy (multivariable adjustment)	OR =1	1.45 (0.77–2.74)	2.88 (1.13–7.43)
	Cross-sectional; 996 Hispanic Americans without history of diabetes	Prevalence of retinopathy (adjusted for age and sex)	OR =1	1.23 (0.64–2.36)	3.32 (1.61–6.86)
		Prevalence of retinopathy (multivariable adjustment)	OR =1	1.34 (0.68–2.62)	3.58 (1.70–7.53)

Abbreviations: HbA1c, glycated hemoglobin; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

of this analysis was the quite low number of subjects with HbA_{1c} ≥6.5%.

Should there be ethnicity-specific thresholds of the HbA_{1c} for the diagnosis of diabetes?

As mentioned in the introduction, HbA_{1c} levels vary considerably with ethnicity. In particular, Blacks have higher HbA_{1c} levels than Whites at any glycemic level, and therefore, higher thresholds for Blacks have been discussed. The question whether there are ethnic differences in the association between HbA_{1c} and prevalent retinopathy was examined in two recent cross-sectional studies.[36,41]

In nondiabetic participants of the NHANES study, the mean HbA_{1c} level was lowest in non-Hispanic Whites (5.5%), and highest in non-Hispanic Blacks (5.7%); for Hispanic Americans, it was 5.6%.[41] When subjects with HbA_{1c} ≥6.5% were compared to subjects with HbA_{1c} <5.7%, the age–sex adjusted odds ratios (ORs) for retinopathy were 1.22 (95% CI 0.47–3.16), 2.71 (95% CI 1.06–6.93), and 3.32 (95% CI 1.61–6.86), respectively, in non-Hispanic Whites, non-Hispanic Blacks, and Hispanic Americans. Although the two latter ORs were much larger than the OR for non-Hispanic Whites, the interaction term between ethnicity and level of HbA_{1c} was not statistically significantly related to the prevalence of retinopathy (P=0.72), and this was also found after further multivariable adjustment. Therefore, the authors see no support for ethnic-specific HbA_{1c} thresholds.

In another analysis of NHANES data, a significant increase in the risk of diabetic retinopathy was seen at lower levels of HbA_{1c} in Blacks than in Whites; the risk of retinopathy started to increase in Blacks with HbA_{1c} 5.5%–5.9% and in Whites with HbA_{1c} 6.0%–6.4%.[36] From this, the authors drew the conclusion that the HbA_{1c} threshold to diagnose

diabetes should not be increased in Blacks. From the results of this study alone, one might even draw the conclusion that the threshold of the HbA_{1c} should even be lower for Blacks than Whites. We assume that the authors did not go that far given the strong evidence that HbA_{1c} levels are generally higher in Blacks than in Whites.

Conclusion

Identification of HbA_{1c} thresholds for the diagnosis of diabetes is mainly based on studies of the association between HbA_{1c} levels and retinopathy because retinopathy is the most diabetes-specific complication. For other microvascular complications, associations with HbA_{1c} are too weak, as far as this can be seen from the very few available cross-sectional studies. For macrovascular complications, HbA_{1c} is only one among various other strong risk factors. Thus, identification of thresholds mainly relies on one single microvascular complication which covers only a small part of the burden of type 2 diabetes mellitus complications.

The existing studies on the association between HbA_{1c} and retinopathy have important drawbacks. Most studies are cross-sectional, subjects with known diabetes have often not been excluded, confounders (like age, sex, blood pressure) are often not adjusted for. Cutoffs suggested by these studies vary widely from 5.2%–7.8%, and thresholds depend strongly on statistical methods, on definition of retinopathy, and the distribution of HbA_{1c} in the study group. Even for a given data set, cutoffs differ widely with regard to the statistical method. The whole of the studies suggests that the recommended 6.5% threshold has mainly been brought about by convention rather than having a consistent empirical basis.

By now, we recommend a somewhat pragmatic access, which is to examine how well the 6.5% criterion does at distinguishing subjects with retinopathy from subjects without retinopathy. The few studies which allow an answer to this question indicate that the prevalence of any retinopathy is 2.5 to 4.5 times higher in subjects with $HbA_{1c} \geq 6.5\%$ than in subjects with lower HbA_{1c} levels. For severe retinopathy, these factors are even much higher. In some cross-sectional studies, prevalence of any retinopathy was quite high, even for $HbA_{1c} < 6.5\%$, ie, 10.7% in the Reykjavik study and 6.4% in the Malay study.[20,35] However, any retinopathy may also have nondiabetic reasons, and moreover, these studies were done in older study groups.

There is still another reason why the HbA_{1c} threshold should be dealt with in a pragmatic way. Many doctors do not follow guidelines and do not strictly follow the criteria for the diagnosis of diabetes. In a study in US veterans done before the recommendation of the new HbA_{1c} criteria, it was shown that only 2% of doctors met the criteria of diagnosing diabetes recommended at that time.[42] Nevertheless, 4 years later, 88% of the patients who had received a diagnosis of diabetes actually had $HbA_{1c} \geq 6.5\%$ or received diabetes medication. Obviously, the predictive accuracy is much larger than the diagnostic accuracy. Thus, in the real world, criteria for the diagnosis of diabetes do not have to be perfect but in some way reasonable to work within clinical practice. In this regard, the 6.5% threshold seems to be a sensitive, pragmatic solution. However, there is a strong need for longitudinal studies on the associations between HbA_{1c} and microvascular complications with subjects free of diabetes and diabetes complications at baseline. Only if such studies gave a strong indication for other HbA_{1c} thresholds should the discussion on the best HbA_{1c} cutoff be reopened.

Disclosure

The authors declare no conflicts of interest in this work.

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