

# Use of GHb (HbA<sub>1c</sub>) in Screening for Undiagnosed Diabetes in the U.S. Population

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**OBJECTIVE** — To evaluate the use of GHb as a screening test for undiagnosed diabetes (fasting plasma glucose  $\geq 7.0$  mmol/l) in a representative sample of the U.S. population.

**RESEARCH DESIGN AND METHODS** — The Third National Health and Nutrition Examination Survey included national samples of non-Hispanic whites, non-Hispanic blacks, and Mexican Americans aged  $\geq 20$  years. Of these subjects, 7,832 participated in a morning examination session, of which 1,273 were excluded because of a previous diagnosis of diabetes, missing data, or fasting time of  $< 8$  h before examination. Venous blood was obtained to measure fasting plasma glucose and GHb in the remaining 6,559 subjects. Receiver operating characteristic curve analysis was used to examine the sensitivity and specificity of GHb for detecting diabetes at increasing GHb cutoff levels.

**RESULTS** — GHb demonstrated high sensitivity (83.4%) and specificity (84.4%) for detecting undiagnosed diabetes at a GHb cutoff of 1 SD above the normal mean. Moderate sensitivity (63.2%) and very high specificity (97.4%) were evident at a GHb cutoff of 2 SD above the normal mean. Sensitivity at this level ranged from 58.6% in the non-Hispanic white population to 83.6% in the Mexican-American population; specificity ranged from 93.0% in the non-Hispanic black population to 98.3% in the non-Hispanic white population.

**CONCLUSIONS** — GHb is a highly specific and convenient alternative to fasting plasma glucose for diabetes screening. A GHb value of 2 SD above the normal mean could identify a high proportion of individuals with undiagnosed diabetes who are at risk for developing diabetes complications.

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Although GHb is widely accepted as a useful index of mean blood glucose in the treatment of patients with diabetes, its use as a screening test for diabetes has been controversial. Because GHb testing can be performed at any time of day and with-

out special patient preparation, it is more convenient for patients and health care providers than oral glucose tolerance tests (OGTTs) or even measuring fasting plasma glucose. However, some reports have suggested that GHb may not be a suitable

screening test because of low sensitivity (1–8); others have suggested the opposite (9–21). Although the American Diabetes Association (ADA) recommends the use of GHb as a baseline test before initiating therapy (22), ADA does not currently recommend the use of GHb for diabetes screening or diagnosis (23).

Two recent developments have prompted the reevaluation of GHb as a screening test for diabetes. First, the National Glycohemoglobin Standardization Program (NGSP), implemented in 1996, standardizes GHb results among methods and laboratories (24). Second, the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, published in 1997, included new criteria for diabetes diagnosis that have been adopted by ADA (25). The new criteria lowered the fasting plasma glucose cutoff for diabetes diagnosis from 7.8 mmol/l (140 mg/dl) to 7.0 mmol/l (126 mg/dl) and emphasized the use of fasting plasma glucose rather than the OGTT for diagnosing diabetes. The Expert Committee also recommended that all individuals aged  $\geq 45$  years and younger individuals at high risk for developing diabetes be screened at regular intervals.

Herein, we examine the sensitivity and specificity of GHb for diabetes screening in a large and representative U.S. population by using the new ADA criteria of fasting plasma glucose  $\geq 7.0$  mmol/l as the cutoff for diabetes diagnosis.

**RESEARCH DESIGN AND METHODS** — The Third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The survey included a nationally representative sample of the U.S. civilian noninstitutionalized population with oversampling of non-Hispanic blacks and Mexican Americans (26). A total of 23,258 subjects aged  $\geq 20$  years were eligible for the survey, of which 18,825 completed a household interview that included questions to determine whether they had

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Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; DCCT, Diabetes Control and Complications Trial; NGSP, National Glycohemoglobin Standardization Program; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Classification of subjects for ROC analysis

	Fasting plasma glucose classification	
	Normal or IFG (<7.0 mmol/l)	Diabetes ( $\geq$ 7.0 mmol/l)
HbA <sub>1c</sub> $\leq$ cutoff level	TN	FN
HbA <sub>1c</sub> > cutoff level	FP	TP
	Sensitivity: $TP/(TP + FN) \times 100$	
	Specificity: $TN/(TN + FP) \times 100$	

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

previously been diagnosed with diabetes. Of these subjects, 16,573 participated in a physical examination that included measurement of GHb and fasting plasma glucose; approximately half ( $n = 7,832$ ) were assigned to and participated in a morning examination session and were asked to fast for at least 9 h before examination. Subjects who were assigned to or participated in afternoon or evening examinations ( $n = 8,741$ ), subjects in the morning session who reported a previous diagnosis of diabetes ( $n = 632$ ), subjects who had fasted <8 h before their examination ( $n = 351$ ), and subjects who had data missing ( $n = 290$ ) were excluded from analysis. No statistically significant differences were evident between individuals excluded from the analysis and those included in the analysis (27). Of the remaining individuals ( $n = 6,559$ ), 2,789 were non-Hispanic white, 1,752 were non-Hispanic black, 1,751 were Mexican American, and 267 were from other racial or ethnic groups. Of these subjects, 2,871 belonged to a subset of individuals aged 40–74 years who were given an OGTT in which plasma glucose was measured at 2 h after administration of a 75-g oral glucose load.

GHb was measured as HbA<sub>1c</sub> by using an ion-exchange high-performance liquid chromatography method (Bio-Rad Diamat; Hercules, CA) interassay coefficient of variation 2%) (28). Fasting and 2-h plasma glucose levels were measured by using a hexokinase enzymatic method (Roche Cobas Mira, Indianapolis, IN) (28). Subjects were classified as having normal fasting plasma glucose (<6.1 mmol/l), impaired fasting glucose (6.1–6.9 mmol/l), or diabetes ( $\geq$ 7.0 mmol/l) based on the recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (25). The weighted mean HbA<sub>1c</sub> for patients with normal fasting plasma glucose (<6.1 mmol/l,  $n = 5,694$ ) was  $5.17 \pm 0.45\%$  (mean  $\pm$  SD). We examined the sensitivity and specificity of HbA<sub>1c</sub> to classify subjects as having undiag-

nosed diabetes by using cutoffs of 1, 2, 3, and 4 SD above the normal mean.

Statistical analysis was performed by using SAS (Cary, NC) and SPSS (Chicago) software packages. The NHANES III sampling design involved unequal probabilities of selection and planned oversampling of blacks and Mexican Americans (26). For this reason, the NHANES III Mobile Examination Center morning session final weight was used in analyses so that estimates would reflect a representative U.S. population (29). Logistical regression analysis was used to model the probability that subjects would be classified as having diabetes as a function of their HbA<sub>1c</sub> value. For the analysis, ADA's criteria for diagnosis of diabetes with fasting plasma glucose were used as the "gold standard" (i.e., subjects with fasting plasma glu-

cose  $\geq$ 7.0 mmol/l were classified as having diabetes, whereas subjects with fasting plasma glucose <7.0 mmol/l were classified as not having diabetes). The results were summarized with receiver operating characteristic (ROC) analysis to examine the sensitivity and specificity of HbA<sub>1c</sub> for detecting diabetes at increasing HbA<sub>1c</sub> cutoff levels (30). Table 1 summarizes the classification of subjects for the ROC analysis. Sensitivity at each possible HbA<sub>1c</sub> cutoff level was calculated as  $[TP/(TP + FN)] \times 100$ , where TP = true positive (diabetic fasting plasma glucose and HbA<sub>1c</sub> cutoff level) and FN = false negative (diabetic fasting plasma glucose,  $\leq$  cutoff level HbA<sub>1c</sub>). The sensitivity represents the percentage of those with fasting plasma glucose <7.0 mmol/l who are classified as positive according to HbA<sub>1c</sub>. Specificity was calculated as  $[TN/(TN + FP)] \times 100$ , where TN = true negative (nondiabetic fasting plasma glucose and  $\leq$  cutoff level HbA<sub>1c</sub>) and FP = false positive (nondiabetic fasting plasma glucose, >cutoff level HbA<sub>1c</sub>). The specificity represents the percentage of those with fasting plasma glucose <7.0 mmol/l who are classified as negative according to the HbA<sub>1c</sub>. The ROC curve plots the sensitivity against 1 minus the specificity at all possible HbA<sub>1c</sub> cutoff levels. The higher the area under the curve (AUC),

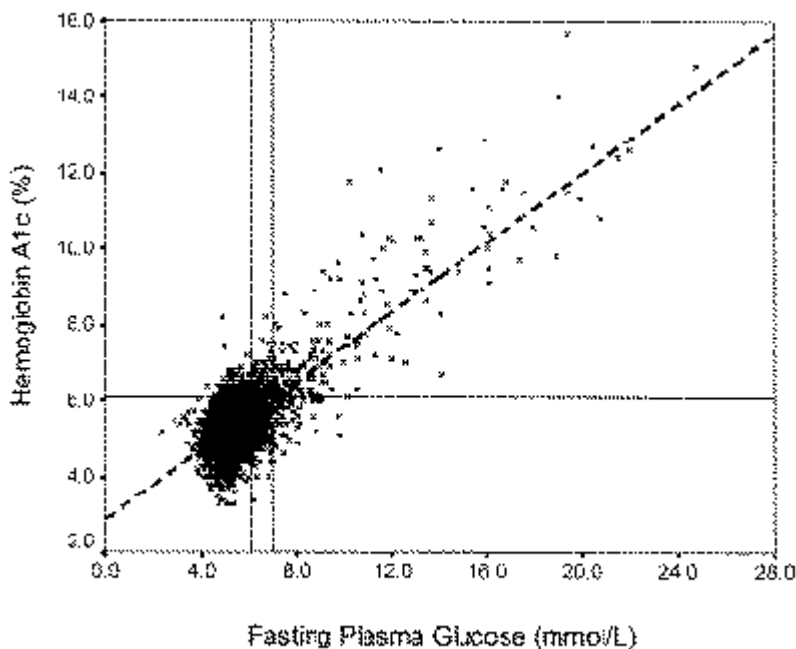


Figure 1—Scatter plot of individuals according to their HbA<sub>1c</sub> and fasting plasma glucose values. HbA<sub>1c</sub> and fasting plasma glucose were linearly related, and the linear regression line had a correlation coefficient of 0.74. The vertical lines are drawn at fasting plasma glucose levels of 6.1 mmol/l (110 mg/dl) and 7.0 mmol/l (126 mg/dl). The horizontal line is drawn at an HbA<sub>1c</sub> level of 6.1% (2 SD above the mean for subjects with a fasting plasma glucose level <6.1 mmol/l).

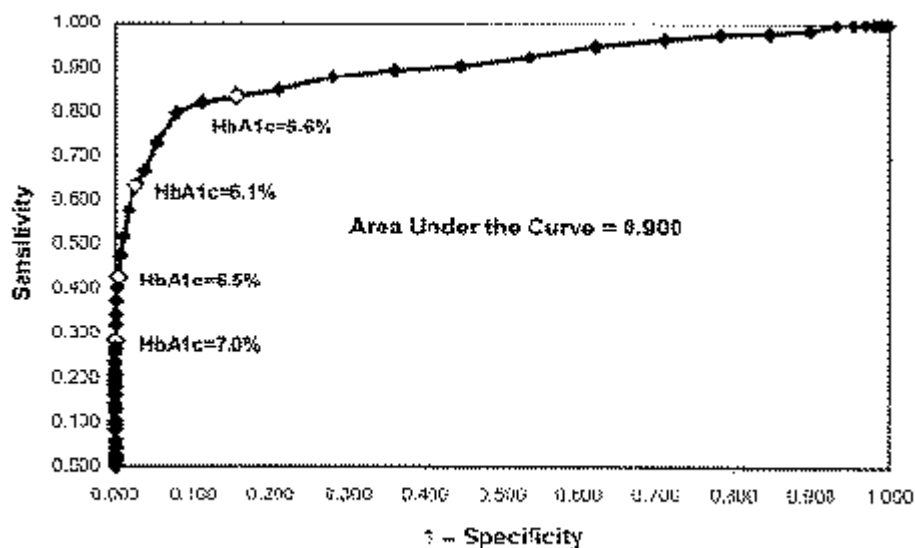


Figure 2—ROC curve for HbA<sub>1c</sub> as a diagnostic indicator for diabetes (fasting plasma glucose  $\geq 7.0$  mmol/l).  $\blacklozenge$ , Each possible HbA<sub>1c</sub> cutoff level;  $\diamond$ , cutoffs of 1, 2, 3, and 4 SD above the normal mean.

as estimated by the *c* statistic, the better the predictive value of HbA<sub>1c</sub> based on the logistical regression model. An AUC value of 0.500 would indicate no predictive value, whereas a value of 1.000 would indicate perfect predictive value with no false positives or false negatives.

**RESULTS** — Figure 1 is a plot of individuals according to their HbA<sub>1c</sub> and fasting plasma glucose values. HbA<sub>1c</sub> and fasting plasma glucose were linearly related, and the linear regression line had a correlation coefficient of 0.74. Figure 2 shows the ROC plot representing the sensitivity and specificity of HbA<sub>1c</sub> in detecting undiagnosed diabetes at each possible HbA<sub>1c</sub> cutoff level. The analysis revealed a high predictive value for HbA<sub>1c</sub> in detecting undiagnosed diabetes; the AUC was 0.900 (Fig. 2).

Table 2 shows the weighted sensitivity and specificity of HbA<sub>1c</sub> for detecting undiagnosed diabetes at HbA<sub>1c</sub> cutoff levels of 1, 2, 3, and 4 SD above the mean HbA<sub>1c</sub> for normal subjects (fasting plasma glucose  $< 6.1$  mmol/l). As the number of standard deviations increased, sensitivity decreased, and specificity increased. HbA<sub>1c</sub> demonstrated high sensitivity (83.4%) and specificity (84.4%) for detecting undiagnosed diabetes at an HbA<sub>1c</sub> cutoff of 1 SD above the normal mean. Moderate sensitivity (63.2%) and very high specificity (97.4%) were evident at an HbA<sub>1c</sub> cutoff of 2 SD above the normal mean.

Characteristics of subjects who were above or below an HbA<sub>1c</sub> value of 6.1%

(2 SD above the normal mean) were investigated further. A total of 265 subjects had a diabetic fasting plasma glucose value ( $\geq 7$  mmol/l). Of these, 193 had an HbA<sub>1c</sub> level of  $> 6.1\%$ . Of the 72 subjects with an HbA<sub>1c</sub> level of  $\leq 6.1\%$ , 21 had fasting plasma glucose values that were very close (7.0–7.2 mmol/l) to nondiabetic values. Additionally, 24 of 46 subjects in this group for whom 2-h plasma glucose results were available showed nondiabetic ( $< 11.1$  mmol/l or  $< 200$  mg/dl) 2-h plasma glucose values.

A total of 6,294 subjects had nondiabetic fasting plasma glucose values ( $< 7.0$  mmol/l). Most of these ( $n = 6,024$ ) had an HbA<sub>1c</sub> level of  $\leq 6.1\%$ . However, 270 subjects had an HbA<sub>1c</sub> level of  $> 6.1\%$  ( $> 2$  SD above the normal mean), and 54 had an HbA<sub>1c</sub> level of  $> 6.5\%$  ( $> 3$  SD above the normal mean).

Table 3 shows the sensitivity and specificity of HbA<sub>1c</sub> at a cutoff value of 6.1% (2 SD above the normal mean) by

racial and ethnic group. The estimated sensitivity was higher in the non-Hispanic black and Mexican-American populations than in the non-Hispanic white population. The estimated specificity was slightly higher in the non-Hispanic white and Mexican-American populations than in the non-Hispanic black population.

The sensitivity of HbA<sub>1c</sub>  $> 6.1\%$  for detecting impaired fasting glucose was low (13.4%), although the estimated mean HbA<sub>1c</sub> was higher for those with impaired fasting glucose compared with those with normal fasting glucose (5.59 vs. 5.17%).

**CONCLUSIONS** — We previously studied the use of GHb as a screening test in a Pima Indian population with a high prevalence of type 2 diabetes and found high sensitivity and specificity for detecting diabetes compared with the OGTT (21). In the present study, we demonstrate that GHb is both sensitive and specific for detecting undiagnosed diabetes as defined by a fasting plasma glucose level  $\geq 7.0$  mmol/l (126 mg/dl) in a large and representative U.S. population sample.

We found indications of some differences in the sensitivity and specificity of GHb among ethnic groups. A higher prevalence of diabetes among the non-Hispanic black and Mexican-American populations compared with the non-Hispanic white population has been well described (27), but further studies are needed both to confirm and explain why GHb has better sensitivity as a screening test in these high-risk populations.

The ADA Expert Committee recommended that screening for diabetes be accomplished primarily by measuring fasting plasma glucose. However, fasting is inconvenient for patients, and subjects do not always fast properly, which can lead to misdiagnosing diabetes (31). In contrast, GHb can be measured at any time of the day regardless of the length of fast or the content of the previous meal. Moreover,

Table 2—Sensitivity and specificity of HbA<sub>1c</sub> for detecting undiagnosed diabetes (fasting plasma glucose  $\geq 7.0$  mmol/l) at increasing HbA<sub>1c</sub> cutoff levels

HbA <sub>1c</sub> cutoff (%)	Sensitivity	Specificity
5.6 (1 SD above normal mean)	83.4	84.4
6.1 (2 SD above normal mean)	63.2	97.4
6.5 (3 SD above normal mean)	42.8	99.6
7.0 (4 SD above normal mean)	28.3	99.9

Data are %.

Table 3—Sensitivity and specificity of HbA<sub>1c</sub> at 6.1% for detecting undiagnosed diabetes (fasting plasma glucose  $\geq 7.0$  mmol/l) by race and ethnicity

Race and ethnicity	n	Sensitivity	Specificity
Non-Hispanic white	2,789	58.6	98.3
Non-Hispanic black	1,752	75.8	93.0
Mexican American	1,751	83.6	97.8
Other	267	68.1	94.7

Data are n or %.

GHb can be analyzed with a small amount of sample, as little as 5  $\mu$ l of blood obtained from a fingerstick (32). Blood can even be collected on filter paper and sent to a central laboratory for analysis (33) when screening individuals who live in remote areas.

GHb is a more comprehensive measure of total glycemic exposure than fasting plasma glucose in that it is a measure of plasma glucose not only in the fasting state but also in the postprandial state. Hence, it may be a better predictor of glycemia-related complications. GHb is highly correlated with the presence of diabetic microvascular complications in prospective studies (20,25,34–37), and McCance et al. (20) further demonstrated that GHb is as effective a predictor of microvascular complications as fasting plasma glucose. The Expert Committee did not select GHb as the screening or diagnostic method because of “the many different methods for the measurement of GHb” and because “nationwide standardization of the GHb test had just begun” (25). However, the National Glycohemoglobin Standardization Program has obviated these issues by making standardization of GHb methods widely available (24). The NGSP certifies manufacturers’ GHb testing methods as traceable to the Diabetes Control and Complications Trial (DCCT) reference. Therefore, results from NGSP-certified methods are comparable between methods and laboratories, as demonstrated by recent College of American Pathologists survey data (38), and can be directly related to DCCT-determined risks for the development of microvascular complications. The ADA has recommended that only NGSP-certified methods be used to measure GHb (39), and most of the major GHb assay methods currently in use are certified by the NGSP (40).

In summary, GHb is a highly specific and convenient method to use in screening for undiagnosed diabetes. A GHb value of 2 SD above the normal mean could identify

a large proportion of individuals with undiagnosed diabetes who are at risk for developing diabetes complications.

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