Relationship Between Fasting Plasma Glucose and Glycosylated Hemoglobin Potential for False-Positive Diagnoses of Type 2 Diabetes Using New Diagnostic Criteria

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The rationale for the former diagnostic criteria of diabetes, which have been accepted by both the National Diabetes Data Group1 and the World Health Organization,2 was that the specific microvascular complication of retinopathy would subsequently develop in a much larger proportion of individuals whose glucose concentrations exceeded the values defining diabetes mellitus than those with lower levels. Specifically, the previous World Health Organization criteria for diabetes were a fasting plasma glucose (FPG) concentration of 7.8 mmol/L (140 mg/dL) or more, or an oral glucose tolerance test (OGTT) result (2-hour plasma glucose concentration following 75 g of oral glucose) of 11.1 mmol/L (200 mg/dL) or more. The corresponding criteria for impaired glucose tolerance were an FPG concentration of less than 7.8 mmol/L (140 mg/dL) or more, or an OGTT result (2-hour plasma glucose concentration following 75 g of oral glucose) of 7.8 mmol/L (140 mg/dL) or more. The cutpoints selected were based on 3 prospective studies in which 1213 subjects were given an OGTT, 77 of whom developed retinopathy 3 to 8 years later.3-5

Context New criteria for the diagnosis of type 2 diabetes mellitus have recently been introduced that lowered the diagnostic fasting plasma glucose (FPG) concentration from 7.8 to 7.0 mmol/L (140 to 126 mg/dL).

Objective To determine if individuals with diabetes diagnosed by the new FPG concentration criterion would have excessive glycosylation (elevated hemoglobin [HbA1c] levels).

Definitions We determined the distribution of HbA1c levels in individuals using 4 classifications: (1) normal by the new criterion (FPG concentration <6.1 mmol/L [110 mg/dL]); (2) impaired fasting glucose by the new criterion (FPG concentration of 6.1-6.9 mmol/L [110-125 mg/dL]); (3) diabetes diagnosed solely by the new FPG concentration criterion of 7.0 through 7.7 mmol/L (126-139 mg/dL); and (4) diabetes diagnosed by the previous FPG concentration criterion of 7.8 mmol/L (140 mg/dL) or higher.

Design Cross-sectional analysis of 2 large data sets (NHANES III and Meta-Analysis Research Group [MRG] on the Diagnosis of Diabetes Using Glycated Hemoglobin) that contained individuals in whom FPG concentrations, 2-hour glucose concentrations using an oral glucose tolerance test, and an HbA1c level were simultaneously measured. We cross-tabulated FPG concentrations (<6.1 mmol/L [110 mg/dL], 6.1-6.9 mmol/L [110-125 mg/dL], 7.0-7.7 mmol/L [126-139 mg/dL], and ≥7.8 mmol/L [140 mg/dL]) and HbA1c levels separated into 3 intervals: normal, less than the upper limit of normal (ULN); slightly elevated, ULN to ULN plus 1%; and high, higher than ULN plus 1%.

Results Among subjects with normal FPG concentrations, HbA1c levels in the NHANES III (and the MRG) data sets were normal in 97.3% (96.2%), slightly elevated in 2.7% (3.6%), and high in 0.1% (0.2%). Among individuals with impaired fasting glucose, HbA1c concentrations were normal in 86.7% (81.4%), slightly elevated in 13.1% (16.4%), and high in 0.2% (2.2%). Among diabetic patients diagnosed by the new FPG criterion only, HbA1c levels were normal in 18.6% (16.7%), slightly elevated in 32.5% (32.8%), and high in 48.9% (62.3%). Among diabetic patients diagnosed by the former FPG criterion, HbA1c levels were normal in 16.7%, slightly elevated in 32.5% (21.0%), and high in 48.9% (62.3%).

Conclusions About 60% of the new cohort of diabetic patients in both data sets have normal HbA1c levels. We believe that diabetes should not be diagnosed in those with FPG concentrations less than 7.8 mmol/L (140 mg/dL) unless excessive glycosylation is evident. Individuals without excessive glycosylation but with moderate elevations of FPG concentrations (6.1-7.7 mmol/L [110-139 mg/dL]) should be diagnosed as having impaired fasting glucose and treated with an appropriate diet and exercise. This diagnostic labeling achieves the goal of early intervention without subjecting these persons to the potentially negative insurance, employment, social, and psychological consequences of a diagnosis of diabetes mellitus.

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We agree with the logic that the diagnosis of diabetes should be based on levels of glycosylation that are associated with the development of specific microvascular complications (eg, retinopathy). In recent years, excessive glycosylation of a variety of proteins has been widely accepted to be a major (albeit probably not the sole) pathogenic factor in the microvascular and neuropathic complications of diabetes. Of more importance, aminoguanidine, a molecule that inhibits advanced glycosylation before irreversible cross-linking occurs, prevented or lessened the formation of both advanced glycosylation end products and diabetes-related complications in vivo in diabetic animals. Two other inhibitors of advanced glycosylation, a monoclonal antibody against Amadori-modified glycosylated albumin and a novel thiazolidine derivative, significantly reduced advanced glycosylation end products and slowed the development of diabetic nephropathy and retinopathy in 2 animal models of diabetes. Although intervention trials in humans have not been completed, there is a strong association in both humans and animals between the microvascular and neuropathic complications of diabetes and excessive glycosylation, as well as proof of causation in animals. Finally, there was a quantitative in-vivo link between glycosylated hemoglobin (HbA1c) levels and advanced glycosylation end product formation in human red blood cells. This compelling evidence is the basis for physicians to use glycosylated hemoglobin levels to monitor the results of treatment.

In 1995, the Expert Committee (EC) on the Diagnosis and Classification of Diabetes Mellitus, convened by the American Diabetes Association, reexamined both the diagnosis and classification of diabetes in light of any new information available since the 1979 report of the National Diabetes Data Group. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. The new criteria for the diagnosis of diabetes are: (1) symptoms of diabetes and casual plasma glucose concentration of 11.1 mmol/L (200 mg/dL) or higher (casual is defined as any time of day without regard to time since last meal); or (2) FPG of 7.0 mmol/L (126 mg/dL) or higher (fasting is defined as no energy intake for at least 8 hours); or (3) 2-hour plasma glucose of 11.1 mmol/L (200 mg/dL) or more during an OGTT (the test should be performed as described by the World Health Organization using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water). In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure listed above is not recommended for routine clinical use. The new approach eliminates the OGTT in routine clinical practice and lowers the threshold for diagnosing diabetes by the FPG concentration from 7.8 to 7.0 mmol/L (140 to 126 mg/dL). The EC also defined a normal FPG concentration as less than 6.1 mmol/L (110 mg/dL) and values of 6.1 to 6.9 mmol/L (110-125 mg/dL) as impaired fasting glucose (IFG).

Due to the importance of glycosylation in the pathogenesis of the microvascular complications and the development of these (especially retinopathy) to define the criteria for diabetes, individuals with normal glycosylated hemoglobin levels, in our view, should not be considered to have diabetes. Because glycosylated hemoglobin levels are used to judge therapy, their treatment with diet and exercise would be no different than in those with lower FPG concentrations. Labeling these individuals as people with diabetes exposes them to potentially negative insurance, employment, social, and psychological consequences and creates more harm than benefit. Therefore, we examined the distribution of HbA1c levels in the patients diagnosed as having diabetes by the new criteria only (ie, those with FPG concentrations of 7.0-7.7 mmol/L [126-139 mg/dL]). We also compared the distribution of HbA1c levels in those whose diagnosis was changed from diabetes to IFG by the new criteria. For example, a patient with 2-hour value from the OGTT of 11.1 mmol/L (200 mg/dL) or more but whose FPG concentration was lower than 7.0 mmol/L (126 mg/dL) was diagnosed as having diabetes by the old criteria but IFG by the new vs a patient with a 2-hour OGTT value that was lower than 11.1 mmol/L (200 mg/dL) but with an FPG concentration of 7.0 to 7.7 mmol/L (126-139 mg/dL) who was diagnosed as having diabetes by the new criterion.

METHODS

We used 2 data sets to examine the consequences of the change in definition of diabetes. The third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994 was designed to assess the health of the nation. The other data set used was the Meta-Analysis Research Group (MRG) on the Diagnosis of Diabetes using Glycated Hemoglobin containing the pooled results of 10 studies in which FPG concentrations, 2-hour values from OGTT, and HbA1c levels were simultaneously measured.

NHANES III is a national health survey that includes historical, physical, and laboratory examination of subjects selected through a stratified multistage, probability-cluster sampling design. It is designed to provide data representative of the US population. Subjects in NHANES III who met the following criteria were identified using STATA 5.0 (STATA Corp, College Station, Tex) in accordance with the method described by Harris et al: (1) age between 40 and 74 years, (2) no known history of diabetes (other than gestational diabetes), (3) appropriately fasted overnight, and (4) fasting, 2-hour 75-g postglucose load and HbA1c measurements taken according to protocol.

Subjects were identified in the 11 276 population MRG data set if they had fasting and 2-hour postglucose load measurements and whose glycosylated hemoglobin levels were measured by ion exchange chromatography (HbA1c). When required (because some of the studies used 50-g glucose...
loads or measured capillary whole blood glucose), values were transformed to represent venous plasma values before and 2 hours after 75 g of glucose. We defined normal glucose tolerance according to the new criteria (ie, an FPG concentration <6.1 mmol/L [110 mg/dL] and a 2-hour glucose value following a 75-g oral glucose load of <7.8 mmol/L [140 mg/dL]). We defined the normal range for HbA1c in each data set separately, including only those subjects who met these fasting and 2-hour criteria. The upper limit of normal (ULN) of HbA1c was defined as mean plus 2 SDs.

For each data set, we cross-tabulated FPG concentrations lower than 6.1 mmol/L (110 mg/dL), 6.1 to 6.9 mmol/L (110 to 125 mg/dL), 7.0 to 7.7 mmol/L (126 to 139 mg/dL), and 7.8 mmol/L (140 mg/dL) or higher with HbA1c levels of less than ULN, ULN to ULN plus 1%, and greater than ULN plus 1%. In the MRG data set there was no weighting, each subject contributed equally. In NHANES III, we used their WTPFD6 weighting variable to render HbA1c distributions representative of the US population in this age group. This variable adjusts the distribution to account for the intentional oversampling of minority populations and reconstitutes a distribution representative of the age and ethnic and racial makeup of the United States. We divided elevated HbA1c values into 2 intervals of ULN to ULN plus 1% and more than ULN plus 1% for the following reasons: (1) patients whose glycosylated hemoglobin levels are less than ULN plus 1% do not have or have little development or progression of retinopathy or nephropathy, (2) patients with glycosylated hemoglobin levels of 1% above the ULN or more have 90% to 95% chance of meeting the OGTT criteria for diabetes, and (3) individuals with lesser degrees of hyperglycemia (ie, those with IFG or impaired glucose tolerance) almost always have glycosylated hemoglobin levels of less than 1% above the ULN.

We were interested in 2 theoretical groups of patients whose diagnostic status would differ whether they presented for diabetes screening before or after implementation of the new recommendations. For example, if patients in the first group had FPG levels of less than 7.0 mmol/L (126 mg/dL) their levels would not meet the criterion for diabetes. But if they had elevated 2-hour glucose values from OGTTs of more than 11.1 mmol/L (200 mg/dL) their values would meet the old criteria for a diagnosis of diabetes. However, if these patients presented for screening under the new recommendations, the OGTT would not be performed, their 2-hour value would remain unknown, and they would be deemed not to have diabetes on the basis of their FPG concentrations. We call these persons the newly normal group. If the second group has FPG concentrations of 7.0 to 7.7 mmol/L (126-139 mg/dL) with 2-hour glucose values from the OGTT of less than 11.1 mmol/L (200 mg/dL), they would not have diabetes by the old criteria (since their FPG concentrations are <7.8 mmol/L [140 mg/dL] and their 2-hour glucose values on the OGTT are <11.1 mmol/L [200 mg/dL]), but would be diagnosed as having diabetes by the new criterion (since their fasting glucose concentrations are ≥7.0 mmol/L [126 mg/dL]). We refer to these persons as the newly diabetic group. Thus, we wanted to compare the prevalence of excessive glycosylation in the newly diabetic with the newly normal group. If the new diagnostic recommendations represent an improvement, the prevalence of excessive glycosylation should be higher in the newly diabetic group than in the newly normal group. To perform this analysis, we identified subjects in the 2 databases who met these fasting and 2-hour criteria and compared the number of subjects and the distribution of HbA1c levels in each group.

**RESULTS**

There were 2836 persons in the NHANES III data set who met inclusion criteria. There was a mean (SD) of 5.3% (0.4%) HbA1c level of the 1846 subjects with normal glucose tolerance (FPG <6.1 mmol/L [110 mg/dL] and 2-hour glucose values <11.1 mmol/L [140 mg/dL]). Therefore, the normal range (mean ± 2 SD) was 4.4% to 6.1% in the NHANES III population. After weighting the population sample, these normal subjects represented 71% of the US population not already known to have diabetes. A normal glucose tolerance was found in 6952 (78%) of the 8917 subjects in the MRG data set, whose glycosylated hemoglobin levels were measured in an HbA1c assay. The mean (SD) HbA1c level in these subjects was 5.1% (0.6%). Therefore, the normal range in the MRG population was 3.9% to 6.3%.

The relationship of FPG concentrations to HbA1c levels was similar in the 2 data sets (TABLE and FIGURE 1). For simplicity, and because they are population-based, only NHANES III data are presented in the text. Excessive glycosylation was rare in those with normal FPG concentrations (<3% of the population), and while 13% of those with IFG (FPG concentrations 6.1-6.9 mmol/L [110-125 mg/dL]) had mild elevations in HbA1c levels (0.2%-7.0%), less than 0.2% of this group had marked elevations in HbA1c levels (≥7.1%). The distribution of HbA1c levels in subjects diagnosed as having diabetes with FPG values between 7.0 and 7.7 mmol/L (126-139 mg/dL) (the newly diabetic group was defined as those with 2-hour values <200 mg/dL, but some had 2-hour values >200 mg/dL) was closer in shape to the distribution of those with IFG (FPG concentrations 6.1-6.9 mmol/L [110-125 mg/dL]) than those with unquestionable diabetes (FPG concentrations >7.7 mmol/L [139 mg/dL]). While the prevalence of mildly increased glycosylation is similar in this group and those having diabetes by the old fasting criterion (about 34%), the prevalence of high HbA1c levels in the new cohort of diabetic patients is roughly 3%, which is a value much closer to the 0.2% seen in those with IFG than the 49% seen in those with FPG concentrations of more than 7.7 mmol/L (139 mg/dL).

Seventy-three percent of individuals who would be diagnosed as having dia-
false-positive diagnoses of diabetes mellitus

The third National Health and Nutrition Examination Survey (NHANES III) data set had 2836 subjects and the Meta-Analysis Research Group data set had 8917 subjects. Despite their disparate origins (the NHANES III data set was a population-based sample whereas the MRG data set was aggregated from 10 published studies), the results from each were remarkably similar. Sixty percent of individuals in both data sets diagnosed as having diabetes by the new criterion only (ie, those with FPG concentrations of 7.0 to 7.7 mmol/L [126-139 mg/dL] and 2-hour OGTT glucose value of less than 11.1 mmol/L [200 mg/dL]) for every 3 individuals who had diabetes solely by the 2-hour OGTT glucose value (≥11.1 mmol/L [200 mg/dL]) but not by the new FPG concentration criterion (ie, fasting values <7.0 mmol/L [126 mg/dL]). Of course, these latter patients were mostly unidentified because OGTT results were often not used to make the diagnosis of diabetes.

**Comment**

Despite their disparate origins (the NHANES III data set was a population-based sample whereas the MRG data set was aggregated from 10 published studies), the results from each were remarkably similar. Sixty percent of individuals in both data sets diagnosed as having diabetes by the new criterion only (ie, those with FPG concentrations of 7.0-7.7 mmol/L [126-139 mg/dL]) had a normal HbA1c level (Table). This congruence gives added credibility to these findings. Furthermore, these cohorts had only a 3.4% to 7.6% chance of having a level of glycosylation that is associated with much development or progression of the microvascular complications.42-46 As stated in the EC's report,38 “determining the optimal diagnostic level of hyperglycemia depends on a balance between the medical, social, and economic costs of making a diagnosis in someone who is not truly at substantial risk."

### Table. Distribution of Hemoglobin A1c Levels According to Fasting Plasma Glucose Concentrations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>National Health and Nutrition Examination Survey (NHANES III) Data Set</th>
<th>Meta-Analysis Research Group Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemoglobin A1c, %</td>
<td></td>
</tr>
<tr>
<td>Fasting Plasma Glucose Level, mmol/L (mg/dL)</td>
<td>No. of Subjects† (%)</td>
<td>No. of Subjects‡ (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>≤6.1 6.2-7.0 7.1</td>
<td>≤6.3 6.4-7.2 7.3</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>2284 (84) 97.3 2.7 0.1</td>
<td>7908 (89) 96.2 3.6 0.2</td>
</tr>
<tr>
<td>Diabetes by new fasting criterion only</td>
<td>77 (2) 60.9 35.8 3.4</td>
<td>131 (1) 59.6 32.8 7.6</td>
</tr>
<tr>
<td>Diabetes by old and new fasting criterion</td>
<td>≥7.8 (140) 102 (3) 18.6 32.5 48.9</td>
<td>276 (3) 16.7 21.0 62.3</td>
</tr>
</tbody>
</table>

To convert hemoglobin A1c from percentage of total hemoglobin to proportion of total hemoglobin, multiply by 0.01.†Based on the US population after weighting the population actually studied, which oversampled minorities.

82% of individuals in the newly normal group (2-hour OGTT values ≥11.1 mmol/L [200 mg/dL] and FPG concentration <7.0 mmol/L [126 mg/dL]) had normal glycosylation, with 18% having mild elevations and only 0.3% with high values. Based on the number of individuals in each data set who had the FPG and 2-hour values described above, we estimated that implementation of the new criterion labels 1 additional person as having diabetes by virtue of an FPG concentration from 7.0 to 7.7 mmol/L (126-139 mg/dL) and a 2-hour OGTT glucose value of less than 11.1 mmol/L (200 mg/dL) for every 3 individuals who had diabetes solely by the 2-hour OGTT glucose value (≥11.1 mmol/L [200 mg/dL]) but not by the new FPG concentration criterion (ie, fasting values <7.0 mmol/L [126 mg/dL]). Of course, these latter patients were mostly unidentified because OGTT results were often not used to make the diagnosis of diabetes.

![Figure 1. Distribution of Hemoglobin A1c Levels by Fasting Plasma Glucose](image1)

![Figure 2. Distribution of Hemoglobin A1c Levels in Those Diagnosed as Having Diabetes Mellitus by New and Old Criteria](image2)
risk of the adverse effects of diabetes and those of failing to diagnose someone who is.” Since treatment is linked to measures of excessive glycosylation, we believe that giving individuals with normal glycosylated hemoglobin levels the diagnosis of diabetes will lead to more harm than benefit (eg, employment, insurance, and possibly social and psychological disadvantages). In fact, people diagnosed as having diabetes are 8 times more likely to be unable to obtain medical insurance because of poor health or illness than people without diabetes.

Three studies (Figures 3 through 5) were offered in support of the lowered FPG concentration to make the diagnosis of diabetes in the EC’s report. The most apparent aspect of all 3 studies is that unlike blood pressure and cholesterol levels for which risk increases continuously even in the normal range, there is a threshold above which the risk for diabetic retinopathy increases markedly. The value of that threshold is the issue. In the EC’s report, only the minimum values of each decile were presented. Although we do not know the individual values of those patients with retinopathy in the initial decile of increased prevalence, it is extremely unlikely that most of them congregated at the lower end of the decile. We have included the mean and maximum values for each decile as well as the number of individuals within each decile in Figures 3 through 5.

In the Pima Indian study depicted in Figure 3, both longitudinal and cross-sectional data were compiled in 960 subjects aged 25 years or older. The increase in retinopathy occurred in the ninth decile in which the minimum and mean FPG concentrations were 7.6 mmol/L (136 mg/dL) and 9.3 mmol/L (168 mg/dL), respectively. Although the minimum value might be considered consistent with the EC’s recommendation that the diagnosis of diabetes could be made by FPG concentrations below 7.8 mmol/L (140 mg/dL), the mean value, which is much more likely to reflect the threshold value for retinopathy in this decile, is certainly not.

In the Egyptian study shown in Figure 4, cross-sectional data were collected in 1018 subjects. The prevalence of diabetic retinopathy increased in the eighth decile in which the minimum and mean FPG concentrations were 7.2 mmol/L (130 mg/dL) and 8.6 mmol/L (155 mg/dL), respectively. Again, although the minimum value could be considered consistent with the new FPG concentration criterion for the diagnosis of diabetes, the mean value is more consistent with the older one of 7.8 mmol/L (140 mg/dL).

In unpublished results from the NHANES III study depicted in Figure 5, cross-sectional data were collected on 2821 subjects between the ages of 40 and 74 years. The increase in retinopathy occurred in the 10th decile whose lowest value for the FPG concentration was 6.7 mmol/L (120 mg/dL). The mean value for the FPG concentration in the 10th decile was 9.2 mmol/L (165 mg/dL). The minimum FPG value would seem to be the strongest support for the EC’s recommendation. However, as noted in the other 2 studies in Figures 3 and 4, the less misleading mean value validates the older FPG criterion.

Note that these deciles and the prevalence rates of retinopathy differ considerably among the studies, especially the Egyptian study, in which diabetic subjects were oversampled. Retinopathy was ascertained by different methods in each study. Therefore, the absolute prevalence rates are not comparable among studies, but their relationships with FPG, 2-hour plasma glucose, and HbA1c levels are similar within each population.

What would be lost by classifying people whose FPG concentrations are 7.0 to 7.7 mmol/L (126-139 mg/dL), but with normal HbA1c levels, as having IFG instead of diabetes? Most clinicians

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would agree that if a patient’s glycosylated hemoglobin level were less than 1% above the ULN for the assay used (<7.1% in the NHANES III population), control is satisfactory and no change in therapy is necessary. Therefore, the diabetic patients diagnosed solely by the new criterion would be given nutritional counseling and exercise advice, not pharmacological agents. This would occur whether they carried the diagnosis of diabetes or IFG.

The virtually identical distributions of HbA1c levels in patients newly diagnosed as having diabetes and those whose diagnosis is now changed from diabetes to either IFG or normal (Figure 2) supports this approach. We have not changed the therapy in either group, only their diagnoses. The disadvantages of the diagnosis of diabetes are removed from one cohort and imposed on the other. We do not favor the return of the OGTT, but do favor an approach to the diagnosis of diabetes that consistently identifies equal risks for the microvascular and neuropathic consequences of hyperglycemia and one that can justify the potentially negative insurance, employability, and social and psychological costs. 48-50

The NHANES data set (Table) and the latest available census data53 allow calculation of the number of individuals in the population between ages 40 and 74 years who would now be diagnosed as having diabetes because their FPG concentrations are 7.0 to 7.7 mmol/L (126-139 mg/dL). There were 260 million people living in the United States in 1994, of whom 90 million fell in the 40- to 74-year age range. Two percent or 1.8 million of them now have diabetes but 60% or 1.1 million have normal glycosylated hemoglobin levels and 36% or 648 000 have mildly elevated HbA1c levels of a degree that would require only nonpharmaceutical intervention. It is likely that the percentage of people in this category would be even higher in the population exceeding age 74 years.

Given the importance of excessive glycosylation in the genesis and development of diabetic complications6-37 in determining the threshold values for the diagnosis of diabetes, we would like to suggest an alternative approach to the diagnosis of diabetes (Figure 6). This approach uses measurements of FPG concentrations followed by glycosylated hemoglobin levels in individuals whose values are neither normal (<6.1 mmol/L [110 mg/dL]) nor meet the old criterion for the diagnosis of diabetes (≥7.8 mmol/L [140 mg/dL]). A glycosylated hemoglobin level determines whether an individual with an FPG concentration of 6.1 to 7.7 mmol/L (110-139 mg/dL) has diabetes or a milder degree of hyperglycemia. A persistent glycosylated hemoglobin level of 1% above the ULN or more for the assay used makes the diagnosis of diabetes. A lower value makes the diagnosis of IFG, which is a high-risk category for the future development of diabetes (and possibly cardiovascular disease). In this approach, individuals with FPG concentrations of 7.0 to 7.7 mmol/L (126-139 mg/dL) will be identified and treated appropriately with diet and exercise, but they will not be given the diagnosis of diabetes.

Although it is argued that current glycosylated hemoglobin assays are not yet standardized and therefore should not be used for the diagnosis of diabetes,38 the potential error certainly cannot approach 60%. This is the proportion of the cohort of diabetic patients diagnosed solely by the new criterion who have normal glycosylated hemoglobin levels. These individuals, in our view, will carry a false-positive diagnosis of diabetes. In regard to using HbA1c levels to diagnose diabetes in people with elevated FPG concentrations (Figure 6), it is of interest that the mean values in the deciles in which retinopathy markedly increased in the Pima Indian,51 Egyptian,52 and unpublished data from the NHANES III58 studies were 7.8%, 7.5%, and 7.4%, re-

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**Figure 4.** Prevalence of Retinopathy in Egyptians

![Image of graph showing prevalence of retinopathy in Egyptians](image-url)

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose, mg/dL</th>
<th>Minimum</th>
<th>Mean</th>
<th>Maximum</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9</td>
<td>6.2</td>
<td>9.9</td>
<td>12.5</td>
<td>102</td>
</tr>
</tbody>
</table>

*To convert FPG concentrations from milligrams per deciliter to millimoles per liter, multiply by 0.05551. Data adapted from Engelgau et al.52*
respectively. All these values are more than 1% above the ULN. Finally, using the NHANES III data, Rohlfing and colleagues suggest that a precise glycosylated hemoglobin assay is both sensitive and specific for detecting diabetes.

Several limitations of our data are noteworthy. First, the data are cross-sectional and although the NHANES III study is population-based, we are unable to longitudinally determine the relationship of glucose or Hba1c levels to the development of microvascular complications of diabetes. Second, both data sets only measured glucose concentrations once. Since the diagnostic criterion requires 2 independent fasting samples above 6.9 mmol/L (125 mg/dL) to diagnose diabetes, this could lead to misclassification of some individuals as having diabetes. However, the magnitude of this phenomenon is insufficient to appreciably change our results.

In conclusion, 60% of the cohort of diabetic patients diagnosed solely by the new diagnostic criterion (ie, those with FPG concentrations of 7.0-7.7 mmol/L [126-139 mg/dL]) will have normal glycosylated hemoglobin levels and one third will have values less than 1% above the ULN. Because excessive glycosylation plays such a prominent role in the pathogenesis of diabetic microvascular complications, the development of which are used to set the diagnostic criteria, we feel that a diagnosis of diabetes in this setting is a false-positive one. A reasonable alternative approach (albeit not yet rigorously tested) to the diagnosis of diabetes is using measurements of FPG concentrations followed by Hba1c levels in individuals whose FPG values are 6.1 to 7.7 mmol/L (110-139 mg/dL).

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REFERENCES

4. Sayegh HA, Jarrett RJ. Oral glucose-tolerance tests and the diagnosis of diabetes: results of a prospec-

Figure 5. Prevalence of Retinopathy in the Third National Health and Nutrition Examination Survey

Figure 6. Alternative Approach to the Diagnosis of Diabetes Mellitus
false-positive diagnoses of diabetes mellitus

5. Pettitt DJ, Knowler WC, Lisse JR, Bennett PH. De-
velopment of retinopathy and proteinuria in relation to plasma-glucose concentrations in Pima Indians. Lan-
6. Bucala R, Cerami A, Vlassara H. Advanced glyco-
ylation end products in diabetic complications. Dia-
7. Cefalu WT, Wang ZQ, Bell-Farrow A, Ralapati S. Liver and kidney tissue membranes as tissue markers for nonenzymatic glycosylation. Diabetes. 1991;40:
902-907.
8. Mitsuhashi T, Nakayama H, Itobe T, et al. Immuno-
chemical detection of advanced glycation end prod-
cuts in renal cortex from STZ-induced diabetic rat. Dia-
betes. 1993;42:826-832.
9. Tarso JF, Wigness B, Rhode TD, Rupp WM, Buchwal H, Furcht LT. Nonenzymatic glycation of fi-
bronectin and alterations in the molecular associ-a-
tion of cell matrix and basement membrane compo-
nents in diabetes mellitus. Diabetes. 1985;34:477-
484.
10. McLennan S, Yue DK, Swanson MB, Delbridge L, Reeve T, Turtle J. The prevention and reversibility of tissue non-enzymatic glycosylation in diabetes. Dia-
11. Vlassara H, Brownlee M, Cerami A. Nonenzy-
matic glycosylation of peripheral nerve protein in dia-
betes mellitus. Proc Natl Acad Sci U S A. 1981;78:
5190-5192.
12. Vlassara H, Brownlee M, Cerami A. Excessive non-
enzymatic glycosylation of peripheral and central ner-
vous system myelin components in diabetic rats. Dia-
13. Sensi M, Prici F, Pugliese G, et al. Role of advanced glycation end-products (AGE) in late diabetic compli-
14. Uitto J, Perejda AJ, Grant GA, Rowold EA, Kilo S. Immunological detection of advanced glycation end prod-
cuts in streptozocin-induced diabetic rats. J Clin Invest. 1993;91:2463-
2469.
16. Beisswenger PJ, Makita Z, Curphey TJ, et al. For-
mation of immunohemochromatogen advanced glycosylation end products precedes and correlates with early manifes-
tations of renal and retinal disease in diabetes. Dia-
90:6434-6448.
19. Kaneshige H. Nonenzymatic glycosylation of se-
20. Lutjens A, Te Velde AA, Te Veen EA, Meer J. Gly-
cosylation of human fibrinogen in vivo. Diabetologia.
21. Ono Y, Aoki S, Ohnishi K, et al. Increased serum levels of advanced glycation end-products and diabe-
41:131-137.
23. Clements RS Jr, Robison WG Jr, Cohen MP. Anti-
glycated albumin therapy ameliorates early retinal mi-
crovascular pathology in db/db mice. J Diabetes Com-
24. Nakamura S, Makita Z, Ishikawa S, et al. Progression of nephropathy in spontaneous diabetic rats is pre-
25. Wolffenbuttel BHR, Giordano D, Founds HW, Bu-
cala R. Long-term assessment of glucose control by haemoglobin AGE measurement. Lancet. 1996;347:
513-515.
26. Report of the Expert Committee on the Diagno-
27. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eb-
erhardt MS. Comparison of diabetes diagnostic cat-
egories in the US population according to 1997 Ameri-
20:1859-1862.
28. Harris MI, Flegal KM, Cowie CC, et al. Preval-
ence of diabetes, impaired fasting glucose, and im-
29. Peters AL, Davidson MB, Schirger DL, Hassel-
blad V. A clinical approach for the diagnosis of dia-
30. DCCT Research Group. The effect of intensive dia-
betes treatment on the development and progres-
32. Diabetes Control and Complications Trial Re-
search Group. The relationship of glycemic exposure (HgbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Compli-
1255.
34. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, To-
35. Davidson MB, Peters AL, Schirger DL. An alterna-
36. Tattersall RB, Jackson JCL. Social and emotional complications of diabetes. In: Keen H, Jarrett J, eds. Compli-
37. Knowler WC. Screening for NIDDM: opportuni-
ties for detection, treatment and prevention. Diabe-
38. Harris MI. Health insurance and diabetes. In: Na-
600. No. 95-1468.
39. McCance DR, Hanson RL, Charles MA, et al. Com-
parison of tests for glycated haemoglobin and fast-
ting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994;308:
1323-1328.
40. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose level diagnoses of diabetes: diagnostic criteria and per-
fice; 1995.

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that can achieve reversal of ocular vasospasm as well as improvement of ocular circulation. In the last 30 years many publications have attested that (a) ocular blood flow is compromised by glaucoma; (b) the insult responsible can be vasospastic, and therefore reversible; and (c) the extent of vasospasm can be correlated with degree of visual defect. It is irrelevant whether ischemia is the primary insult or a result of increased pressure, since improvement of circulation by treatment with vasodilators such as calcium channel blockers has been shown to benefit glaucoma patients. In addition, reversal of vasospasm using carbon dioxide has also been shown to be effective in a study of low-tension glaucoma patients. We therefore believe that in the future, the most effective glaucoma drug will not only reduce intraocular pressure and inhibit the cascade of events leading to apoptosis but also will ensure adequate circulation in the optic nerve head and reverse ischemia and vasospasm in those locations.

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In Reply: In response to Dr Harris and colleagues, our article was not intended to provide a complete review of the state of the art in the management of and research about glaucoma. We fully recognize the fascinating and significant work that is being done, not only in the field of ocular circulation but in many other aspects of the study of glaucoma. Agents that improve optic nerve blood flow may well become part of the armamentarium in the management of this disease. However, the past 10 years have seen the release and widespread clinical use of many new antiglaucoma agents, such as prostaglandins, clonidine derivatives, topical carbonic anhydrase inhibitors, and novel preparations of topical β-blockers. Newer optic nerve imaging and visual-field technologies have been developed, allowing for more accurate and earlier diagnoses. Major breakthroughs have been made in our understanding of the genetics of glaucoma, discoveries that may someday lead to a cure. The pace of development in glaucoma research is heartening, given the severity and incidence of the disease.

In our brief review, we selected those works that—in our opinion—represent what may be a recent paradigm shift in thinking about the pathophysiology of the glaucomatous process. With a clearer understanding of some of the downstream steps leading to the loss of ganglion cells (listed in our Table 1*), it may be possible to develop novel, neuroprotective strategies.

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CORRECTION

Incorrect Wording: In the Special Communication entitled “Relationship Between Fasting Plasma Glucose and Glycosylated Hemoglobin: Potential for False-Positive Diagnoses of Type 2 Diabetes Using New Diagnostic Criteria” published in the April 7, 1999, issue of THE JOURNAL (1999;281:1203-1210), there was incorrect wording in the column headings in the Table on page 1206. The corrected table is reprinted here.

Distribution of Hemoglobin A1c Levels According to Fasting Plasma Glucose Concentrations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fasting Plasma Glucose Level, mmol/L (mg/dL)</th>
<th>No. of Subjects (%)</th>
<th>Hemoglobin A1c, %</th>
<th>No. of Subjects (%)</th>
<th>Hemoglobin A1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;6.1 (110)</td>
<td>2284 (84)</td>
<td>≤6.1</td>
<td>97.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>6.1-6.9 (110-125)</td>
<td>373 (11)</td>
<td>68.7</td>
<td>13.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes by new fasting criterion only</td>
<td>7.0-7.7 (126-139)</td>
<td>77 (2)</td>
<td>60.9</td>
<td>35.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Diabetes by old and new fasting criterion only</td>
<td>≥7.8 (140)</td>
<td>102 (3)</td>
<td>18.6</td>
<td>32.5</td>
<td>48.9</td>
</tr>
</tbody>
</table>

*To convert hemoglobin A1c, from percentage of total hemoglobin to proportion of total hemoglobin, multiply by 0.01.
†Based on the US population after weighting the population actually studied, which oversampled minorities.

In addition, the following sentences should be added to the acknowledgment on page 1209. We wish to thank all of the investigators who contributed their data to the meta-analysis research data set. A complete list of these investigators has been previously published (JAMA. 1996;276:1246-1252).