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Diagnosing Type 2 Diabetes Mellitus: in Primary Care, Fasting Plasma Glucose and Glycosylated Hemoglobin Do the Job

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Objective. To determine the validity of glycosylated hemoglobin (HbA_{1c}) values as a method to diagnose type 2 diabetes mellitus (DM2) in a population at risk seen in primary care.
Design. Cross-sectional analytical study.
Setting. Data were obtained for the Raval Sud study population (epidemiologic study of alterations in glucose metabolism in a population at risk).
Participants. 454 subjects from this population (mean age, 65±3 years; 52% male) at high risk for DM2, seen at a primary care center, were included in the study.
Main measures. We recorded demographic data and laboratory values for fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and HbA_{1c}. The diagnostic criteria used for DM2 were those published by the WHO in 1999. Values for HbA_{1c} were expressed as the number of standard deviations (SD) above the mean.
Results. Levels of HbA1c correlated with FPG (r=0.72) and glucose levels 2 h after oral glucose overload (r=0.43). Thirty percent of the patients with FPG between 110 and 125 mg/dL had HbA1c values higher than the reference limits. A combined technique based on FPG>125 mg/dL or FPG 110-125 mg/dL with $HbA_{1c} \geq 3$ SD (5.94%) showed a sensitivity of 92% and a specificity of 95%.
Conclusions. When FPG is inconclusive (110-125 mg/dL), an HbA_{1c} value more than 3 standard deviations above the mean (>5.94%) is useful in suggesting a likely diagnosis of diabetes and identifying patients who require treatment.

Key words: Glycosylated hemoglobin. Diabetes mellitus. Diagnosis. Oral glucose overload. Fasting plasma glucose.

DIAGNOSTICANDO LA DIABETES MELLITUS TIPO 2: EN ATENCIÓN PRIMARIA, CON LA GLUCEMIA BASAL Y LA HEMOGLOBINA GLUCOSILADA ES SUFICIENTE

Objetivo. Contrastar la validez de la determinación de la hemoglobina glucosilada (A_{1c}) como método diagnóstico de la diabetes mellitus tipo 2 (DM2) en la población de riesgo en atención primaria.
Diseño. Estudio analítico transversal.
Emplazamiento. Datos recogidos de la población del Estudio Raval Sud (estudio epidemiológico de las alteraciones del metabolismo de la glucosa en la población de riesgo).
Participantes. Se incluyó en el estudio a un total de 454 sujetos de esta población (edad media, 65 ± 13 años; 52% varones), con un elevado riesgo de sufrir DM2, atendidos en el centro de atención primaria.
Mediciones principales. Se recogieron datos demográficos y analíticos (glucemia basal, sobrecarga oral de glucosa y hemoglobina A_{1c}). Se utilizaron los criterios diagnósticos de la DM2 de la Organización Mundial de la Salud de 1999. Los valores de A_{1c} fueron estandarizados en intervalos de desviaciones estándar (DE) por encima de la media.
Resultados. Se detectó una correlación entre la A_{1c} y los valores de glucemia basal (r = 0,72) y a las 2 h de la sobrecarga oral de glucosa (r = 0,43). El 30% de los pacientes con glucemia basal entre 110 y 125 mg/dl presentaó valores de A_{1c} superiores a los límites de referencia. Una técnica combinada de diagnóstico basada en una glucemia basal > 125 mg/dl o de 110-125 mg/dl con una $A_{1c} \geq 3$ DE (5,94%) demostró una sensibilidad del 92% y una especificidad del 95%.
Conclusiones. En sujetos con una determinación de glucemia basal no concluyente (110-125 mg/dl), los valores de A_{1c} por encima de la media +3 DE (> 5,94%) son útiles para orientar el diagnóstico de diabetes e identificar a los que requieren tratamiento.

Palabras clave: Hemoglobina glucosilada. Diabetes mellitus. Diagnóstico. Sobrecarga oral de glucosa. Glucemia basal.

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A commentary follow this article (pág. 000)

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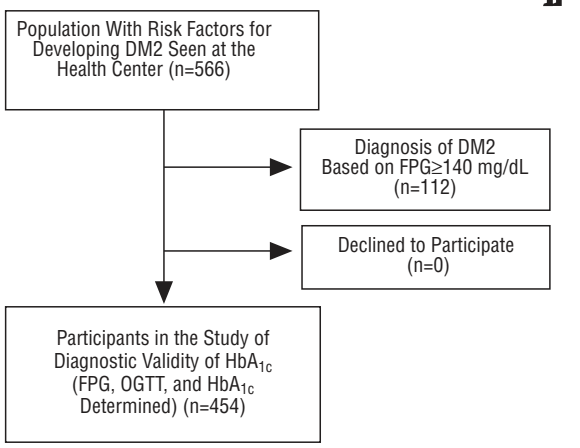
Introduction

The diagnostic criteria for type 2 diabetes mellitus (DM2) as a clinical entity are based on a number of population-based studies that documented a bimodal distribution of plasma glucose concentrations (a continuous laboratory variable), with a higher prevalence of complications typical of DM in the population subgroup with higher values.[1] Statistical procedures were used to artificially dichotomize plasma glucose levels, and a cutoff value was thus set for the diagnosis of DM2.
The diagnostic criteria for diabetes were developed by the National Diabetes Data Group (NDDG)[2] and the World Health Organization (WHO).[3] Later, the American Diabetes Association (ADA),[4] in response to the inconvenience, variability and nonphysiological nature of the oral glucose tolerance test (OGTT), recommended abandoning its routine use in favor of lowering the diagnostic cutoff value for fasting plasma glucose (FPG) to ≥126 mg/dL, which seemed to better predict the risk of developing macrovascular complications.[5,6] In 1999 the WHO included this recommendation in its new diagnostic criteria.[7]
After the discovery that one fraction of hemoglobin in red blood cells (glycosylated hemoglobin, or HbA_{1c}) is elevated in the presence of hyperglycemia lasting for 4-8 weeks, the A_{1c} fraction became the main tool for following metabolic control in persons with diabetes. The importance of this parameter has been reinforced by studies such as the DCCT[8] and the UKPDS,[9] which showed that better control of plasma glucose levels reduced the risk of developing long-term complications.
If diabetes is diagnosed on the basis of plasma glucose values, and if HbA_{1c} accurately reflects plasma glucose levels during the preceding weeks, why not use HbA_{1c} to diagnose DM2? This option has its attractions, because it would obviate the inconvenience and poor reproducibility of the OGTT; moreover, HbA_{1c} correlates well with the likelihood of developing chronic complications. Since this idea was first proposed, different studies have yielded dissimilar results.[6,10] Important drawbacks are the lack of standardization of different methods used to quantify HbA_{1c}, the high cost of this test (placing it beyond the reach of developing countries) and the lack of studies that document the clinical validity of a given diagnostic cutoff point. (It has traditionally been claimed that the diagnostic sensitivity of HbA_{1c} is poor.[11-15])
A group of 18 metaanalyses[16] concluded that although HbA_{1c} cannot be used alone to diagnose diabetes, it is more useful than the OGTT for therapeutic decision-making. One of these articles[17] proposed that diabetes should not be diagnosed in subjects with a fasting plasma glucose concentration lower than 140 mg/dL unless they also had a clearly abnormal level of HbA_{1c}. Patients with moderately elevated FPG (110-139 mg/dL) but without an excessively elevated HbA_{1c} value should be diagnosed as having impaired fasting glucose (IFG) and should be treated with appropriate dietary measures and physical exercise.
The aim of our study was to evaluate the usefulness of HbA_{1c} measurements to diagnose DM2 in a population seen in a primary care center with risk factors for developing DM2.

Material and methods



General Scheme of the Study

Cross-sectional analytical study to determine the diagnostic validity of a strategy based on fasting plasma glucose and HbA_{1c}.

Material and Methods

The study was done at the Raval Sud Primary Care Center in Barcelona. The population served by this center is characterized by its low economic level, high rate of immigration (20%), and high rate of morbidity and mortality for certain diseases and disorders. In addition, 29% of the population is older than 65 years. The recorded prevalence of diabetes is 6.6%, one of the highest rates in Spain.[18]
The Raval Sud study was begun in 1992. This project comprises a number of dynamic cohort studies aimed at documenting the epidemiologic features of glucose metabolism disorders and the rate of appearance of chronic, specific complications. For the purposes of the present study, we used data recorded from the time the patient was included in the Raval Sud program. Consequently, the study used a cross-sectional analytical design to validate a diagnostic test.
Subjects eligible for inclusion in the present analysis had at least one of the risk factors for developing DM2 described in the ADA 1997 guidelines (family history of DM2, personal history of carbohydrate intolerance or gestational diabetes, prolonged

use of a drug able to raise glucose levels, obesity with a body mass index [BMI] >30, hypertension, HDL-cholesterol levels <35 mg/dL, or triglyceride levels >250 mg/dL).[4] We excluded persons who did not wish to take part in the study.

The variables we recorded for each participant were sociodemographic characteristics (age and sex), clinical characteristics (BMI in kg/m^2 and blood pressure in mm Hg, in accordance with the guidelines of the Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure (JNC VI),[28] and laboratory values including FPG in a venous blood sample, OGTT after a 75-g glucose overload (if FPG was lower than 140 mg/dL) in blood samples drawn after 30, 60 and 120 minutes (G2h), and HbA_{1c} measured by high pressure liquid chromatography (HPLC) with a Menarini HA8141 autoanalyzer (normal range =3.8%-5.5%; m=4.65%; SD=0.43%). To standardize the results we recalculated the absolute values of HbA_{1c} in terms of the number of standard deviations above the mean. For example, HbA_{1c}=7.23% was considered equivalent to the mean value +6 SD).

On the basis of FPG and OGTT values we classified the participants according to the WHO 1999 criteria as having normal glucose levels (FPG<110 mg/dL and G2h<140 mg/dL), IFG (FPG, 110-125 mg/dL), impaired glucose tolerance (IGT) (FPG<126 mg/dL and G2h, 140-199 mg/dL), or DM2 (FPG>125 mg/dL or G2h>199 mg/dL).

The sample consisted of 454 subjects. For this sample size and our study conditions (P=.066 and α=.05), the absolute percentage error rate (e) was 2.3%.

The descriptive parameters used for the statistical analysis were the mean, standard deviation (SD) and 95% confidence intervals. Normality of the numerical variables was checked with the Kolmogoroff-Smirnov test. Bivariate analysis was based on chi-squared tests, ANOVA, Pearson's correlation coefficient (r) and their nonparametric counterparts.

Diagnostic value was analyzed by calculating sensitivity, specificity, positive predictive value, negative predictive value, and global value or efficacy (GV) of each cutoff point. "Efficacy" was defined as the proportion of subjects correctly classified with reference to the total number of cases. Predictive values were calculated for a prevalence of 6.6%

TABLE 1 **Distribution of Demographic and Laboratory Variables According to the WHO Diagnostic Classification of DM2 (1999)*,[7]**

	Normal Blood Glucose	IFG	IGT	Diabetes
No pacients	54	32	36	332
Sex				
Male	18	10	14	193
Female	36	22	22	139
Age, years	56.4 (17.6) 58.1 (19.2)	59.1 (13.7)	67.2 (10.4)	
BMI, kg/m^2	28.2 (4.7)	29.3 (4.1)	30.3 (5.2)	29.8 (5.0)
FPG, mg/dL	92 (8.7)	120 (3.4)	107 (15.4)	180 (80)
G2h, mg/dL	107 (20.3)	115 (16.3)	173 (17.5)	223 (55.6)
HbA_{1c}, %	4.98 (0.59)	5.42 (0.45)	5.12 (0.46)	7.04 (2.04)
Total cholesterol, mg/dL	206 (43.2)	235 (33.6)	244 (38.3)	229 (49.1)
HDL-cholesterol, mg/dL	47.3 (11.6)	45.1 (13.0)	44.4 (10.8)	42.5 (11.7)
LDL-cholesterol, mg/dL 135	(37.0)	155 (26.2)	168 (41.7)	154 (46.4)
Triglycerides, mg/dL	124 (65.9)	170 (145)	162 (122)	163 (91)
Systolic BP, mm Hg	131 (21.3)	135 (19.6)	135 (17.4)	143 (21.1)
Diastolic BP, mm Hg	75 (14.0)	77 (13.3)	81 (8.6)	84 (12.0)

*IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; FPG, fasting plasma glucose; G2h, glucose 2 hours after oral glucose overload; HbA_{1c}, glycosylated hemoglobin.

Results

The study included 454 individuals (235 men and 219 women). Mean age was 64.6 (13.2) years, and 20% of the patients were older than 75 years. Mean BMI was 29.63 (4.97) kg/m^2, and 3% of the patients were classified as having morbid obesity (BMI>40 kg/m^2).

The distribution of demographic characteristics and laboratory findings according to the diagnostic classification are shown in Table 1. In the present descriptive analysis we found that plasma glucose values were significantly lower in normal subjects than in subjects with abnormal glucose levels (IFG or IGT), and were in turn lower in the latter group than in patients with diabetes (P<.001). Mean HbA_{1c} was significantly higher in patients with diabetes than in all other categories of participants: 7.04% versus 4.98% (normal glucose level), 5.42% (IFG), and 5.12% (IGT) (P<.001). Patients with IFG had slightly higher HbA_{1c} values than those with IGT, although the difference did not reach statistical significance.

Levels of HbA_{1c} correlated significantly with FPG (r=0.72; P<.001) and glucose measured 30 min (r=0.27; P=.01), 60 min (r=0.39; P<.001) and 2 h (r=0.43; P<.001) after an oral glucose overload.

Table 2 shows the distribution of HbA_{1c} values according to the diagnostic classification. All groups with HbA_{1c} values above 6.37% ($\bar{x}$+4 SD) had DM2, whereas none of the patients with HbA_{1c} below 4.22% ($\bar{x}$−1 SD) had diabetes. Patients with IFG had HbA_{1c} levels that ranged from 4.65% to 6.37% (between the mean value and +4 SD). In the group with IGT, levels of HbA_{1c} were between 4.22% and 6.37% (between −1 SD y +4 SD), and interestingly, HbA_{1c} levels were lower than the mean (between 4.22% and 4.65%) in 8 of the 36 patients with IGT (22%).

TABLE 2 **Distribution of Hemoglobin A1c Values According to the WHO Diagnostic Classification of DM2 (1999)*,[7]**

HbA_{1c}, %	Normal Blood Glucose n = 54	IFG n = 32	IGT n = 36	DM2 n = 332
<3.36 (–3 SD)	0	0	0	0
3.36 to 3.79 (-3 to –2 SD)	0	0	0	0
3.79 to 4.22 (-2 to –1 SD)	0	0	0	0
4.22 to 4.65 (-1 SD to M)	16 (64)	0	8 (32)	1 (4)
4.65 to 5.08 (M to +1 SD)	24 (44)	6 (11)	6 (11)	19 (34)
5.08 to 5.51 (+1 to +2 SD)	10 (10)	18 (17)	16 (15)	61 (58)
5.51 to 5.94 (+2 to +3 SD)	4 (8)	2 (4)	4 (8)	41 (80)
5.94 to 6.37 (+3 to +4 SD)	0	6 (10)	2 (3)	52 (87)
6.37 to 6.80 (+4 to +5 SD)	0	0	0	39 (100)
6.80 to 7.23 (+5 to +6 SD)	0	0	0	12 (100)
7.23 to 7.66 (+6 to +7 SD)	0	0	0	8 (100)
7.66 to 8.09 (+7 to +8 SD)	0	0	0	13 (100)
8.09 to 9.81 (+8 to +12 SD)	0	0	0	50 (100)
>9.81 (+12 SD)	0	0	0	36 (100)

*IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; DM2, type 2 diabetes mellitus.
Percentage values for each range of HbA_{1c} values are shown in parentheses.

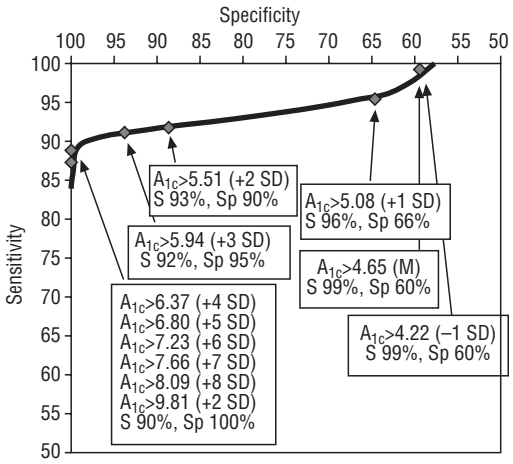


FIGURE 1 ROC curve for the combined strategy (fasting plasma glucose >125 mg/dL or FPG, 110-125 mg/dL + different cutoff points for HbA1c) in diagnosing DM2 according to the WHO criteria (1999)[7].

The diagnosis of DM2 in patients with FPG<110 mg/dL (but with an abnormal OGTT) was rare, accounting for only 1.2% of all cases of DM2. Of the 80 patients with FPG between 110 and 125 mg/dL, 30% had HbA_{1c} values above the normal range (HbA_{1c}>5.5%), 15% had HbA_{1c} levels >5.94% (+3 SD), and none of them had HbA_{1c} levels >6.8% (+5 SD)

Table 3 shows the validity for the entire sample of the different cutoff values of HbA_{1c} in establishing a diagnosis of DM2.

Table 4 shows the diagnostic validity of a combined strategy based on FPG and HbA_{1c} values: patients were considered to have diabetes when FPG>125 mg/dL, or when FPG≥110 mg/dL and HbA_{1c} was abnormally high (≥ the cutoff point). We found that the validity of the HbA_{1c} cutoff points increased markedly as the percentage value increased. Maximal efficacy (93% GV) was found for HbA_{1c}≥5.94% ($\bar{x}$+3 SD), with a sensitivity of 92.2% and a specificity of 95.1%. The Figure illustrates the ROC curve for different HbA_{1c} values.

TABLE 3 **Validity of Different Cutoff Values for Hemoglobin A_{1c} in Diagnosing DM2 in the Whole Sample According to the WHO Diagnostic Criteria (1999)[7]**

HbA_{1c} Value ≥	Sensitivity, %	Specificity, %	Predictive value, %		Global value, %
			Positive	Negative	
4.22% (–1 SD)	100	0	73.1	-	73.1
4.65% (M)	99.7	19.7	77.2	96.0	78.2
5.08% (+1 SD)	94.0	49.2	83.4	75.0	81.9
5.51% (+2 SD)	75.6	85.3	93.3	56.2	78.2
5.94% (+3 SD)	63.3	93.4	96.3	48.3	71.4
6.37% (+4 SD)	47.6	100	100	41.2	61.7
6.80% (+5 SD)	35.8	100	100	36.4	53.1
7.23% (+6 SD)	32.2	100	100	35.2	50.4
7.66% (+7 SD)	29.8	100	100	34.4	48.7
8.09% (+8 SD)	25.9	100	100	33.2	45.8
9.81% (+12 SD)	10.8	100	100	29.2	34.8

Discussion

The present study was done at a primary care center located in the Raval district, a depressed area in downtown Barcelona with particular demographic characteristics. The very low sociocultural level of the population may have led to underdiagnosis of DM2. In addition, mean age of the sample we studied was close to 65 years (64.6 years, with 20% of the sample older than 75 years) and the rate of obesity was high (mean BMI, 29.6 kg/m^2). Standard diagnosis based on FPG and OGTT was used for a selected

population at high risk for developing diabetes. For these reasons the prevalence of DM2 in our sample was much higher than in the general population, but this was expected for a sample of the characteristics described above. We believe this may have made overestimation of the positive and negative predictive values more likely, but probably did not affect the sensitivity or specificity of the different cutoff points in the diagnostic test.

A number of prospective studies have confirmed the relationship between circulating glucose values and the onset of chronic complications.[19-21] It is thus logical for the diagnosis of DM2 to be based on glucose values. The main problem, however, lies in the attempt to establish a cutoff point for this continuous quantitative variable.

A second important problem is the choice of method for measuring plasma glucose that best diagnoses the disease, i.e., that predicts the presence of chronic complications: FPG, postprandial glucose level, OGTT, or 24-hour glucose profile (among other possible tests). Some approaches such as the OGTT are poorly reproducible and highly variable,[22] while others show poor predictive capacity (e.g., a single glucose measurement).[23,24] If hyperglycemia is toxic,[25] it would be logical to use a measure that quantifies the intensity and duration of hyperglycemia—i.e., glycosylated hemoglobin.

The relationship between HbA_{1c} and measures of glucose levels has been widely documented.[5,6,17] In the present study, HbA_{1c} values correlated most clearly with FPG (r=0.72). We also found that FPG and HbA_{1c} appeared to be most useful in detecting diabetes, whereas G2h appeared to be most useful in identifying normal subjects (who have significantly lower values).

As the first step in our test of the usefulness of HbA_{1c} in diagnosing DM2, we analyzed different cutoff points for this laboratory value for the whole sample of patients at risk for DM2. When an HbA_{1c} value of ≥5.51% ($\bar{x}$+2 SD) was used to classify persons as having diabetes, the attendant sensitivity (76%) and specificity (85%) were acceptable. When a higher cutoff point was used, specificity increased, but this was logically at the expense of reduced sensitivity. Differences in the reference populations notwithstanding, our values were similar to those from other studies. For example, Engelgau et al[6] reported that an HbA_{1c} of ≥6.7% had a sensitivity of 68% and a specificity of 99%. The metaanalysis published by Peters et al[16] noted sensitivities of 66% and 36%, with specificities of

TABLE 4 **Diagnostic Validity of a Combined Strategy (Fasting Plasma Glucose >125 mg/dL) or (FPG, 110-125 mg/dL + Different Cutoff Points for HbA_{1c}) in Diagnosing DM2 According to the WHO Diagnostic Criteria (1999)[7]**

HbA_{1c} Value ≥	Sensitivity, %	Spcificity, %	Predictive Value, %		Global Value, %
			Positive	Negative	
4.22% (–1 SD)	98.8	59.7	86.7	94.9	88.1
4.65% ($\bar{x}$)	98.8	59.7	86.7	94.9	88.1
5.08% (+1 SD)	96.4	65.6	88.4	87.0	88.1
5.51% (+2 SD)	92.8	90.2	96.3	82.1	92.1
5.94% (+3 SD)	92.2	95.1	98.1	81.7	93.0
6.37% (+4 SD)	89.8	100	100	78.2	92.5
6.80% (+5 SD)	89.2	100	100	77.2	92.1
7.23% (+6 SD)	89.2	100	100	77.2	92.1
7.66% (+7 SD)	89.2	100	100	77.2	92.1
8.09% (+8 SD)	89.2	100	100	77.2	92.1
9.81% (+12 SD)	89.2	100	100	77.2	92.1

Discussion Key points

What Is Known About the Subject

- The diagnosis of type 2 diabetes mellitus is based on a cutoff value for fasting plasma glucose or plasma glucose after an oral glucose overload that has predictive value for the appearance of complications.
- Glycosylated hemoglobin correlates closely with plasma glucose and the presence of complications.
- The main drawbacks of HbA_{1c} as a method for diagnosing type 2 diabetes mellitus are the lack of standardization of laboratory techniques and insufficient data.

What This Study Contributes

- Glycosylated hemoglobin correlates well with plasma glucose (mainly, fasting plasma glucose) and is in itself a good diagnostic test for type 2 diabetes mellitus (acceptable sensitivity and high specificity).
- A diagnostic strategy based on fasting plasma glucose and HbA_{1c} (FPG>125 mg/dL or FPG, 110-125 mg/dL+HbA_{1c}≥6%) showed excellent diagnostic validity (92% sensitivity and 95% specificity).
- In persons with nondiagnostic fasting plasma glucose values (between 110 and 125 mg/dL) the inconvenience and poor reproducibility of the oral glucose tolerance test can be obviated if HbA_{1c} is measured instead.

98% and 100% for cutoff points of 6.3% ($\bar{x}$+2 SD) and 7.3% ($\bar{x}$+4 SD), respectively. Both of these studies were done in groups consisting exclusively of persons whose diabetes had been diagnosed with OGTT. We opted to use as our reference population all cases of diabetes in the sample (diabetes diagnosed with OGTT or with FPG according to WHO 1999 criteria), as this was a better reflection of the situation encountered in daily practice. A study of a US population (Rohlfing et al)[26] obtained a sensitivity of 63.2% and a specificity of 97.4% with an HbA_{1c} cutoff value of ≥6.1 (+2 SD). Other authors[27] reported similar results. The Japanese Diabetes Society[28] recommended using an HbA_{1c} value of ≥6.1% (+2 SD) as the criterion for diagnosing DM2.

However, one of our aims was to identify a simple, reliable strategy for diagnosis. The OGTT is neither simple nor reliable. In our setting it is rarely requested and almost never used as the basis for therapeutic decisions. Moreover, DM2 is diagnosed only exceptionally when FPG in repeat analyses is below 110 mg/dL (1.2% of all cases of DM2 in the present study).

The study by Ko et al[29] investigated the importance of the OGTT in confirming the diagnosis of DM2. Their results suggested that an OGTT was necessary only for persons with FPG values between 110 and 140 mg/dL and HbA_{1c} values ≥5.5% (with 84% sensitivity and specificity).

Many studies have shown that to diagnose diabetes, measuring HbA_{1c} or FPG is at least as useful as measuring plasma glucose 2 h after an oral glucose overload.[5,16,17,22,23] Tsuji et al[27] reported that simultaneously measuring FPG and HbA_{1c} increased the number of diagnoses in a statistically significant manner in comparison to the use of either of these tests alone.

On the basis of these findings we designed a logical strategy for diagnosis based on current recommendations for FPG values (FPG>125 mg/dL) and the validity of HbA_{1c}, which makes it possible to forgo OGTT when FPG is nondiagnostic (between 110 and 125 mg/dL). In this situation, if HbA_{1c} is ≥5.94% (mean, +3 SD), the diagnosis of DM2 is reliable and accurate in 93% of the cases.

Conclussions

Despite the limitations of this study, we would like to offer some practical considerations that are consistent with the findings of other authors.[5,10.16,17,22,26-29] We believe the combination of FPG and HbA_{1c} values is extremely useful in establishing the diagnosis of diabetes under the following conditions:

– If repeated FPG measurements are above 125 mg/dL, a diagnosis of DM2 should be established, and HbA_{1c} measurement will be needed to evaluate metabolic status and decide on appropriate treatment.

– If repeated FPG measurements are below 110 mg/dL, the individual should probably be considered normal.

– If FPG is between 110 and 125 mg/dL, carbohydrate tolerance may be impaired and HbA_{1c} should be determined. If the result is below the mean +3 SD (<5.94% in the present study), periodic follow-up is advisable with particular attention to risk factors for the appearance of DM2 (obesity, sedentary lifestyle, etc.). If HbA_{1c} is above this value, the patient should be considered diabetic in practical terms. More aggressive health and dietary measures should be started, and short-term pharmacological treatment should probably be considered.

We hope that the not too distant future sees standardization of the laboratory techniques for measuring HbA_{1c}. This would make it possible to readily identify individuals who require intervention to prevent the appearance and progression of diabetes and its complications.

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COMMENTARY

Validity of Diagnostic Tests for Diabetes

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The Raval study published in this issue of ATENCIÓN PRIMARIA reports the first known attempt in Spain to validate the diagnosis of diabetes with glycosylated hemoglobin (HbA_{1c}) values in a population at high risk for diabetes. Different diagnostic methods exist depending on the intent of the study:

1. Epidemiological studies have classically used the oral glucose tolerance test (OGTT) with a single determination 2 hours after the glucose overload.

2. For population screening in the population at high risk for diabetes, fasting plasma glucose (FPG) is usually recommended as a precise, cheap, reproducible and simple test. Many authors have drawn attention to the need to add HbA_{1c} determinations for diagnostic purposes, or to limit the number of subjects who will need an OGTT because their blood glucose level is below the diagnostic threshold but their HbA_{1c} value is above the upper limit of normality (2 SD). This latter strategy would avoid up to 80% of all unneeded OGTT.[1]

Key Points

- The Raval study validates the diagnosis of diabetes with a combination of FPG and HbA_{1c} in a population at high risk for diabetes.
- A national standardization program for HbA_{1c} is needed so that treatment decisions can be based on the same percentage values in accordance with the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), and to facilitate the adoption of a diagnostic cutoff point.
- The Grupo de Estudio de la Diabetes en la Atención Primaria de Salud recommends measuring HbA_{1c} in patients with altered fasting plasma glucose levels, as HbA_{1c} is a good predictor of the appearance of diabetes. A value higher than 2 SD above the mean (upper limit) indicates a high likelihood of diabetes or glucose intolerance, and in these cases an OGTT may be indicated. (This decision may be well grounded, but it is nonetheless a cumbersome test to perform.) This strategy may avoid up to 80% of all OGTT when HbA_{1c} is normal.
- Eliminating the OGTT is controversial, but this test is little used in practice except in pregnant women, for whom it is indispensable.

3. For individual clinical diagnosis, the 1997 American Diabetes Association (ADA) and the 1999 World Health Organization criteria are used. However, these recommendations differ radically with regard to the use of OGTT in persons with impaired fasting glucose (IFG) levels.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the ADA recently decided[2] to reduce the lower limit of normality for FPG from 110 to 100 mg/dL. This decision is aimed at detecting, on the basis of IFG (100 to 125 mg/dL), a number of persons similar to those that would be detected on the basis of impaired glucose tolerance (IGT) who may benefit from lifestyle interventions shown to be effective in delaying the appearance of diabetes. However, this measure is controversial[3] because it fails to take into account the cost/benefit ratio of this decision, which will double the prevalence of IFG[3] (a consequence which itself merits a separate editorial).

TABLE 1 **Limitations of the Oral Glucose Tolerance Test (OGTT)**

High interindividual variability: 16.7%
Low reproducibility compared to fasting plasma glucose: 6.4%
Rarely used in practice
Poor compliance with the conditions needed to perform the test correctly
Cumbersome and time-consuming for nursing staff and patients

Epidemiological studies in different populations were needed to decide whether a cutoff point for FPG of 126 mg/dL is equivalent to a blood glucose value of 200 mg/dL measured 2 hours after oral glucose overload, although these methods do not detect the same patients or have the same diagnostic capacity since they measure different alterations. Many authors continue to consider the OGTT as the best test, given the lack of a better gold standard. However, the use of this test has been justified more on the basis of historical reasons and common accord than because of its intrinsic qualities.[4]

The infrequent use of OGTT in clinical practice (fewer than 20% of all patients with diabetes are diagnosed with this method) and the diagnostic limitations of this method (Table) have led the ADA to advise against its use in favor of FPG, considered the test of first choice. There is no consensus on this point, as the WHO and the European Council still recommend OGTT for patients in the same risk category as IFG to distinguish between persons with IFG only and individuals who fulfill the criteria for diabetes or IGT. This does not seem to be a workable solution given the volume of patients who fulfill the criteria for IFG and the need for a second positive test result. Given the variability in OGTT results[3] (>15%) and its other drawbacks, it is rarely used.

Fasting plasma glucose increases with age from the third to the sixth decade of life, and remains unchanged thereafter.[5] In contrast, plasma glucose 2 hours after a glucose overload is markedly higher in persons older than 65 years.[2,4] There is no evidence of increased insulin resistance that would account for the excess sensitivity of OGTT in older persons, a result that leads to significant differences in the prevalence of diabetes found with each of these two methods. In the San Antonio cohort,[2] persons with OGTT-diagnosed diabetes were fivefold as likely as FPG-diagnosed patients (125 mg/dL) to recover normal glucose tolerance after 7 to 8 years.

The variability of FPG ranges from 5% to 7%.[5] If we consider a biological rate of variation of 6.9% for a true value of FPG of 126 mg/dL, the resulting 95% confidence interval ranges from 109 mg/dL to 143 mg/dL.

In the presence of classical symptoms of diabetes, the diagnosis is usually straightforward, and a single plasma glucose measurement (>200 mg/dL) often suffices. Problems arise, however, in asymptomatic individuals in whom the diagnosis is based exclusively on threshold glucose values that vary from day to day. This justifies the need to confirm the results with a second test. The excessive variabi-

lity of the OGTT justifies the proposal of the ADA expert committee to eliminate this test in favor of FPG. This committee has come out against the proposal to include HbA_{1c} as a new diagnostic method despite its good correlation with the appearance of micro- and macrovascular complications, because its correlation with FPG was not considered sufficiently solid and because of the lack of standardization to ensure that the results are comparable. The committee probably also considered the discrepancies that would arise because of the identification of three different subpopulations depending on the criteria used, a factor that might further confuse the issue.

As an alternative to OGTT, HbA_{1c} could be used instead as a much more reproducible test with a rate of variation lower than 3% (2% in the Raval study). Hemoglobin A_{1c} measurement identifies hyperglycemia present over a period of 12 weeks (as opposed to casual test results indicating hyperglycemia), and when combined with FBG it increases the sensitivity and specificity of the latter.

The limitations of this strategy are mainly its low availability, the lack of a universal standard (95% in the USA; accepted as a diagnostic method in Japan, where the standardization process has been completed; standardization efforts under way in Europe). In the Raval study the normal value was taken as 0.5 points below the reference range of the Diabetes Control and Complications Trial (DCCT), which might explain why the cut point was more than 3 SD above the mean value, when most authors recommend a cut point of 2 SD above the mean.

Another limitation that has been identified but does not appear to affect the conclusions of the study is the fact that HbA_{1c} values are modified by any circumstance that affects the half-life of red blood cells (such as hemoglobin-related disorders, hemolytic anemia or transfusions). This problem is minimized, apparently, with the use of high-pressure liquid chromatography (HPLC).[5]

Are the results of the Raval study applicable to other populations? The present study was done in a population with characteristics that distinguish it from the average situation: older mean age (greater sensitivity of OGTT), 20% immigrants (different ethnic groups) high BMI, and a high (73%) prevalence of diabetes in the population at risk. These factors limit the generalizability of the results. Although sensitivity and specificity did not vary with prevalence, predictive values did, in some cases falling to very low levels. Because of the lack of a standardized procedure for measuring HbA_{1c}, the results can only be extrapolated for now to similar populations and studies that use a HPLC technique similar to that used by Jimeno Mollet and colleagues. A national standardization program for HbA_{1c} is needed so that our treatment decisions can be based on the same percentage values in accordance with the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS), and to facilitate the adoption of a diagnostic cutoff value.

The Diabetes in Primary Health care Study Group (Grupo de Estudio de la Diabetes en la Atención Primaria de Salud, GEDAPS) recommends measuring HbA_{1c} in patients with IFG, as HbA_{1c} is a good predictor of the appearance of diabetes. A value higher than 2 SD above the mean (upper limit) indicates a high likelihood of diabetes or glucose intolerance, and in these cases an OGTT may be indicated. (This decision may be well grounded, but it is nonetheless a cumbersome test to perform.) This strategy may avoid up to 80% of all OGTT when HbA_{1c} is normal.

In any case, within the range of values considered to indicate IFG, a multifactorial approach that considers all cardiovascular risk factors is more efficient and achieves greater reductions in cardiovascular risk than an approach centered exclusively on circulating glucose levels. The clinical identification of the metabolic syndrome, which may course with IFG, IGT or diabetes and influence all risk factors,[6] may be more useful than wasting time distinguishing between glucose regulation disorders that will have little influence on our treatment decisions.

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