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Original article

Performance of Glycated Hemoglobin and a Risk Model for Detection of Unknown Diabetes in Coronary Patients

Jesús M. de la Hera,[a,*] José M. Vegas,[b] Ernesto Hernández,[b] Iñigo Lozano,[a] José M. García-Ruiz,[a] Oliva C. Fernández-Cimadevilla,[a] Amelia Carro,[a] Pablo Avanzas,[a] Francisco Torres,[a] Jeremías Bayón,[a] Teresa Menéndez,[c] Manuel Jiménez-Navarro,[d] and Elías Delgado[c]

[a] *Departamento de Cardiología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[b] *Departamento de Cardiología, Hospital Cabueñes, Gijón, Asturias, Spain*
[c] *Departamento de Endocrinología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[d] *Departamento de Cardiología, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain*

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ABSTRACT

Introduction and objectives: Traditionally, the oral glucose tolerance test has been useful to diagnose unknown diabetes. Recently, the American Diabetes Association committee has accepted glycated hemoglobin ≥6.5% as a criterion for unknown diabetes. The aim was to determine the benefit of glycated hemoglobin for diagnosing unknown diabetes and also create a predictive model that adjusts the indication for oral glucose tolerance test in coronary patients.

Methods: We examined the glycemic profile of 338 coronary patients without previous diagnosis of diabetes, applying 2010 American Diabetes Association criteria. A unknown diabetes risk predictive model was developed using logistic regression analysis, and then validated in another cohort.

Results: Using the glycated hemoglobin criteria and/or fasting plasma glucose, unknown diabetes was diagnosed in 26 patients. The remaining patients were classified according to oral glucose tolerance test as follows: unknown diabetes 53 (17%), prediabetes 144 (46.2%), and normoglycemic 115 (36.8%). The diagnostic method for unknown diabetes was fasting plasma glucose in 25.3%, glycated hemoglobin in 7.6%, and oral glucose tolerance test in 67.1%. A risk model including fasting plasma glucose, glycated hemoglobin, left ventricular ejection fraction, age, and noncoronary vascular disease was shown to effectively predict unknown diabetes after oral glucose tolerance test: area under the ROC curve 0.8 (95% interval confidence: 0.74-0.87). When the oral glucose tolerance test is restricted to patients with a risk score >6 (31% of our sample) we properly identify 83% of unknown diabetes cases (sensitivity: 75%, specificity: 73%, positive predictive value: 40%, negative predictive value: 93%). The model was adequately validated in another cohort of 115 patients (area under the ROC curve 0.84 [95% interval confidence: 0.74-0.95]).

Conclusions: In coronary patients, glycated hemoglobin alone failed to detect many cases of unknown diabetes. However, its inclusion in a risk prediction model leads to optimizing the usefulness of oral glucose tolerance test.

Rendimiento de la glucohemoglobina y un modelo de riesgo para la detección de diabetes desconocida en pacientes coronarios

Palabras clave:
Sobrecarga oral de glucosa
Diabetes mellitus tipo 2
Estimación de riesgo

RESUMEN

Introducción y objetivos: Clásicamente, la sobrecarga oral de glucosa ha diagnosticado la diabetes desconocida. Recientemente, la *American Diabetes Association* ha aceptado un valor de glucohemoglobina ≥ 6,5% como criterio de diabetes desconocida. Pretendemos conocer la rentabilidad que tiene la glucohemoglobina para la detección de diabetes desconocida y validar un modelo que permita ajustar la realización de la sobrecarga oral de glucosa en enfermos coronarios.

Métodos: Se estudia el perfil glucémico de 338 enfermos coronarios sin diabetes conocida. Se usan los criterios de la *American Diabetes Association* de 2010 y, mediante regresión logística, se construye un modelo predictor de diabetes desconocida. Se valida el modelo en otra cohorte.

Resultados: Se diagnosticó diabetes desconocida a 26 enfermos mediante glucohemoglobina y/o glucemia basal. Los demás presentaban, tras realizar sobrecarga oral de glucosa: diabetes desconocida, 53 (17%); prediabetes, 144 (46,2%), y normoglucemia, 115 (36,8%). Método diagnóstico de diabetes desconocida: glucemia basal, 25,3%; glucohemoglobina, 7,6%, y sobrecarga oral de glucosa, 67,1%. Un modelo que incluye glucemia basal, glucohemoglobina, fracción de eyección de ventrículo izquierdo,

* Corresponding author: Departmento de Cardiología, Hospital Universitario Central de Asturias, Julián Clavería s/n, 33006 Oviedo, Asturias, Spain.
E-mail address: jesusdelahera@gmail.com (J.M. de la Hera).

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edad y enfermedad vascular no coronaria resultó eficaz como predictor de diabetes desconocida tras sobrecarga oral de glucosa: área bajo la curva ROC, 0,8 (intervalo de confianza del 95%, 0,74-0,87). Realizando sobrecarga oral de glucosa sólo a la población con puntuación del modelo > 6 (el 31% del total), podemos localizar al 83% de los casos de diabetes desconocida reales (sensibilidad, 75%; especificidad, 73%; valor predictivo positivo, 40%; valor predictivo negativo, 93%). El modelo se validó correctamente en otra cohorte de 115 pacientes (área bajo la curva ROC, 0,84 [intervalo de confianza del 95%, 0,74-0,95]).

Conclusiones: La glucohemoglobina diagnostica aisladamente pocos casos de diabetes desconocida. Sin embargo, su incorporación a un modelo de riesgo permite optimizar la indicación de la sobrecarga oral de glucosa, con un aprovechamiento óptimo.

Abbreviations

A_{1C}: glycated hemoglobin
FPG: fasting plasma glucose
Glu-2 h: glycemia 2 h post-OGTT
OGTT: oral glucose tolerance test
PCI: percutaneous coronary intervention
UDB: unknown diabetes

INTRODUCTION

The incidence of diabetes is rising in the general population[1] and this increase has adverse repercussions on several diseases, resulting in a serious public health problem. Consequently, in recent years many studies have been presented stating the relationship between hyperglycemia and coronary heart disease, from its prognostic value in acute coronary syndrome[2,3] through its high prevalence, not always well diagnosed, in patients with coronary heart diasease.[4,5]

Because of the high prevalence of abnormal glucose metabolism in coronary patients, a high interest in diagnosing unknown diabetes (UDB) is critical. It has been demonstrated that UDB is a predictor of poor prognosis in patients with coronary artery disease.[6] The early diagnosis of UDB would be useful because data suggest that prompt initiation of antidiabetic treatment improves prognosis.[7]

Trying to manage this unsolved problem, the European Society of Cardiology and the European Society for the Study of Diabetes jointly published guidelines[8] which advised to perform an oral glucose tolerance test (OGTT) in all patients without known diabetes diagnosed with a cardiovascular disease (recommendation class I, evidence level B). However, the OGTT is not widely extended in current daily medical practice. Several reasons could explain this fact: economic burden, potential side effects, technical variability,[9] and even different reliability depending on different clinical scenarios.[10,11]

In 2010, due to the widespread use of standardized glycated hemoglobin (A_{1C}) through the National Glycohemoglobin Standardization Program (NGSP)[12], the American Diabetes Association (ADA) finally admitted an A_{1C} value $\geq$6.5% as an additional diagnostic criterion for diabetes.[13]

Until this recent inclusion of A_{1C}, OGTT was the best method for diagnosing UDB. Hence, from a diagnostic benefit point of view, both extending its use to all patients with coronary disease and the time at which the test is performed may constitute controversial issues, especially when we are unsure about the added value of including A_{1C} as a diagnostic criterion for this population.

Our group has already published a study on the detection of UDB after performing OGTT in 338 coronary patients subjected to percutaneous coronary intervention (PCI).[14] The objectives of the present study via further analysis of the aforementioned series are: *a)* to assess the added value of A_{1C} for the diagnosis of UDB in our population, and *b)* to validate a score, using clinical and analytical variables, to optimize the performance of OGTT for those patients at the highest risk of suffering from UDB.

METHODS

Patient Population

The basic methodology of the study has been previously described.[14] In brief, an observational prospective study was conducted via OGTT in a series of consecutive patients revascularized by PCI from November 1, 2005 to May 31, 2006. Patients previously diagnosed with known diabetes, those who underwent primary PCI due to acute coronary syndrome with ST elevation, and those who did not sign the informed consent were excluded from the study (Fig. 1).

During admission, a series of clinical and physical examination data were collected in a clinical interview. At 2 weeks after discharge, a complete metabolic panel was carried out, including an OGTT with 75 g of glucose, basal insulinemia levels, A_{1C} (Adams A_{1C}; Nichols Institute Diagnostics, San Clemente, California, United States), microalbuminury, and lipid, hepatic, and renal profiles. Laboratory studies were performed according to the common practices of the department of biochemistry. Initially measured following the Japanese method, A_{1C} was converted to NGSP units by validated conversion equations[15], using a computer system from our laboratory.

All included patients signed the informed consent, and the study was approved by the research committee from our institution.

Glycometabolic State Stratification

Known diabetes diagnosis was carried out based on the previous diagnosis from the doctor in charge of the patient. The rest of the patients, without known diabetes, were candidates for OGTT. Fasting plasma glucose (FPG) samples were drawn, and then extracted again at 2 h after the intake of 75 g of glucose (Glu-2 h); both were measured in mg/dl.

The ADA 2010 criteria[13] were used for glycometabolic state stratification; patients are classified as follows:

- Normoglycemia: FPG <100 + Glu-2 h <140.
- Impaired fasting glucose: FPG $\geq$100 and <126 + Glu-2 h <140.
- Impaired glucose tolerance: FPG <126 + Glu-2 h $\geq$140 and <200.
- Diabetes: FPG $\geq$126 or Glu-2 h $\geq$200 or A_{1C} $\geq$6.5%.
- Prediabetes: includes impaired fasting glucose and impaired glucose tolerance.

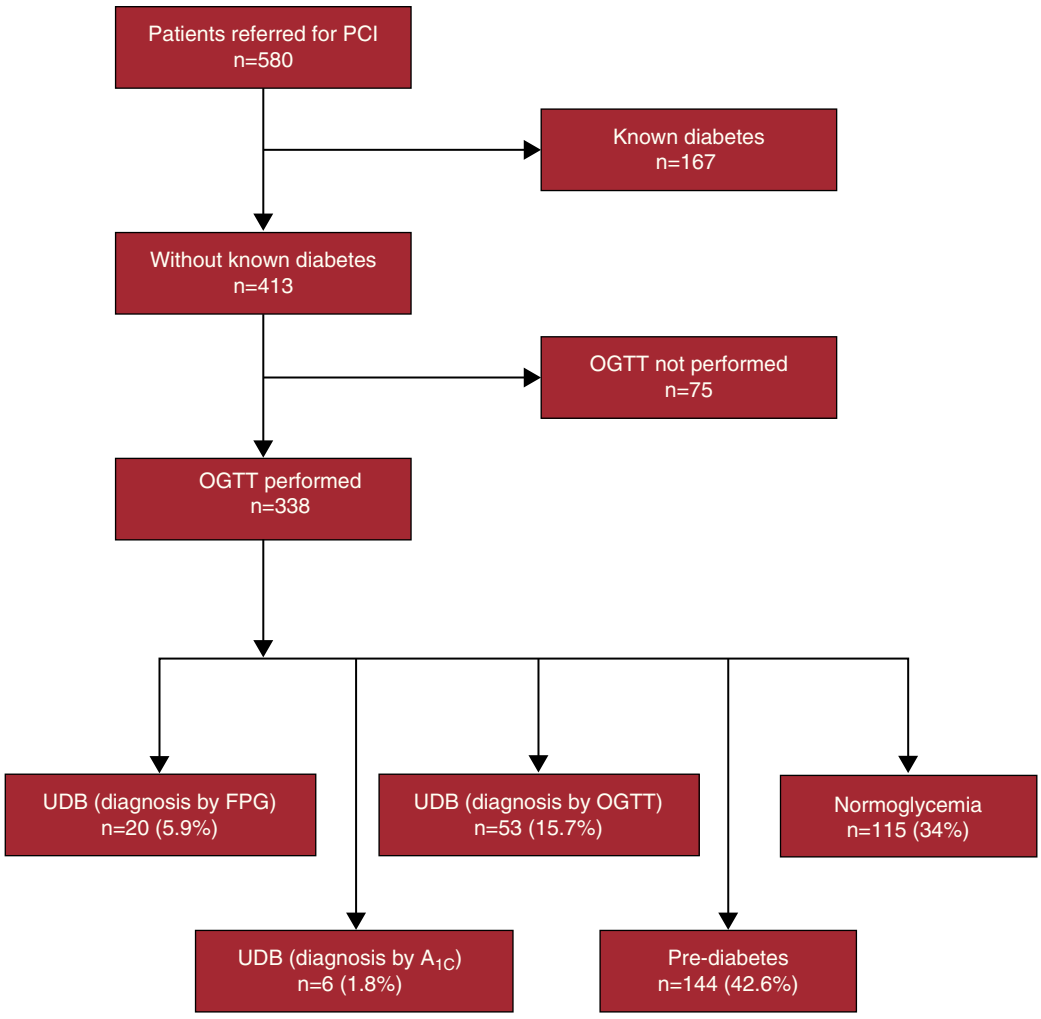

Figure 1. Distribution of the population referred for percutaneous coronary intervention. A_{1C}, glycated hemoglobin; FPG,fasting plasma glucose; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention; UDB, unknown diabetes.

Definition of UDB diagnostic methods:

- UDB diagnosed by FPG, defined as FPG $\geq$126.
- UDB diagnosed by A_{1C}, defined as FPG <126 and A_{1C} $\geq$6.5%.
- UDB diagnosed by OGTT, defined as FPG <126, A_{1C} <6.5%, and Glu-2 h $\geq$200.

Construction and Comparison of the Unknown Diabetes Predictor Model

To create a model that predicts UDB assessed by OGTT, patients with FPG $\geq$126 mg/dl or A_{1C} $\geq$6.5% were excluded since in these cases the diabetes could be diagnosed without the results obtained from the OGTT.

After constructing an UDB predictor model, the benefit of different cut-off points was studied. Furthermore, the diagnostic accuracy of the other 2 models, which restrict the OGTT to patients with impaired fasting glucose based on ADA and World Health Organization (WHO) criteria (FPG >100 and FPG >110 mg/dl, respectively), was tested.

Statistical Analysis

Categorical variables are presented as absolute and relative frequencies, and continuous variables are presented as mean $\pm$ standard deviation. The significance of baseline differences was determined by the χ^2 test, Fisher's exact test, or nonparametric test, as appropriate. A 2-sided P value <.05 was considered to indicate statistical significance. Univariate and multivariate binary logistic regression models were used to determine the contribution of the variables to the endpoint (unknown diabetes). If univariate regression significance was $P < .2$, only the variable judged to be clinically significant was entered into the backward elimination and stepwise multivariate model. Variables included in the multivariate model were age, presence of an acute coronary syndrome, extent of coronary artery disease, left ventricle ejection fraction, A_{1C}, insulin resistance, fasting plasma glucose, noncoronary vascular disease, hypertension, current smoking, and body mass index.

To develop a practical prognostic score, we assigned weighted points proportional to the odds ratio (OR) values (rounded to the nearest integer) to the risk factors identified by multivariate analysis. A risk score was then calculated for each patient, and the population was divided into 3 UDB risk categories: low risk (0 to 5 points), intermediate risk (6 to 10 points), and high risk (11 or more points). We also calculated the sensitivity, specificity, and positive and negative predictive values of our score for different cut-off values in order to compare them with other diagnostic methods for diabetes.

Between January 15 and June 15, 2008, a second series of consecutively admitted patients with coronary disease was registered, although contrary to the first cohort not all the patients

were revascularized. This series was used as a validation cohort; the same clinical and analytical parameters were collected. Finally, we evaluated the score performance to predict UDB in the development cohort and in our independent validation cohort of 115 patients. To assess discrimination, the area under the ROC curve (AUC) was determined. We compared the AUC of the initial cohort against that of the validation cohort, using asymptotic distribution.

RESULTS

Characteristics and Glycometabolic State of the Population

During the study period, PCI was performed in 580 patients, of which 167 were previously diagnosed with known diabetes. Of the patients without previous known diabetes diagnosis, 82% (338/413) underwent OGTT (Fig. 1). In 26 of these 338 patients, UDB could be diagnosed without the 2-h glucose tolerance test (20 had FPG ≥126 mg/dl and 6 had A_{1C} ≥6.5%). The remaining 312 patients were classified as follows: UDB, 17%; impaired fasting glucose, 9%; impaired glucose tolerance, 37.2%; and normoglycemic, 36.8%. The clinical and analytical characteristics of this population are shown in Tables 1 and 2.

Determining Unknown Diabetes Predictors

Independent factors for UDB are shown in Table 3. The most powerful factors in our model were A_{1C} >6.1% (6 points in the score) and FPG >100 mg/dl (5 points). Three points were assigned to the remaining predictive factors (age >65 years, presence of noncoronary vascular disease, and left ventricle ejection fraction <45%). According to the risk of having UDB, we classified patients as follows: <6 points, low probability of UDB (8%); 6-11 points, intermediate probability of UDB (30%); >11 points, high probability of UDB (63%) (AUC: 0.8 [CI 95%, 0.74-0.87]) (Fig. 2).

Diagnostic Benefit of the Different Models

Table 4 shows that the AUC of our model is superior to those models that limit the OGTT if patients meet the impaired fasting glucose criteria of both the WHO and ADA models. In our model, a cut-off point >6 features 75% sensitivity, 73% specificity, 40% positive predictive value, and 93% negative predictive value.

Score Validation

Score validation was performed with a new series of 115 coronary patients without known diabetes. Six of these patients were diagnosed with UDB by FPG, 1 patient by A_{1C}, and the other 108 patients served as a validation cohort. The characteristics of this cohort are shown in Tables 1 and 2.

In the validation cohort, ADA (sensitivity 68%, specificity 73%, AUC 0.69 [CI 95%, 0.57-0.82]) and WHO models (sensitivity 25%, specificity 89%, AUC 0.57 [CI 95%, 0.44-0.71]) do not provide a good discrimination. On the other hand, in our model the patients with <6 points showed a UDB probability of 13%; those with 6-11 points, 32%; those with >11 points, 83%. In this population, the AUC was 0.84 (CI 95%, 0.74-0.95). Figure 2 shows the positive predictive capacity of the model both in the score and the validation cohorts. No differences are found between the AUC for both curves (P = .49).

DISCUSSION

In this study, some interesting findings have been observed: *a)* A_{1C} is not useful by itself for assessing UDB in a population with prior coronary heart disease; *b)* the majority of UDB diagnoses were ascertained by OGTT, and *c)* a risk score using clinical and

Table 1
Clinical Profile of Patients Included in the Score and Validation Cohorts

	Score cohort, 2005-2006 (n = 312)	Validation cohort, 2008 (n = 108)	*P* value
Age (years)	66 ± 18.1	63 ± 22.7	.06
Male sex, no. (%)	251 (80.5)	86 (79.6)	.9
Obesity, no. (%)	115 (36.8)	42 (38.9)	.5
Family history of diabetes, no. (%)	80 (25.6)	15 (13.9)	.01
Waist perimeter (cm)	97.5 ± 10.5	100 ± 10.5	.2
Dyslipidemia, no. (%)	149 (47.7)	60 (55.6)	.16
Hypertension, no. (%)	155 (49.7)	43 (39.8)	.08
Current smoking, no. (%)	86 (27.5)	32 (29.6)	.7
Noncoronary vascular disease, no. (%)	50 (16)	11 (10.2)	.14
Previous MI, no. (%)	118 (37.8)	33 (30.6)	.18
Previous coronary revascularization, no. (%)	47 (15.1)	43 (39.8)	<.001
ACS, no. (%)	240 (76.9)	58 (53.7)	<.001
LVEF	62 ± 8.3	60 ± 12	.3
Treatment at study entry			
β-Blockers, no. (%)	236 (75.6)	84 (78.5)	.51
ACEI/ARB, no. (%)	120 (38.5)	60 (55.5)	.01
Statins, no. (%)	253 (81.1)	100 (92.6)	.01

ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; LVEF, left ventricle ejection fraction; MI, myocardial infarction.
Categorical variables expressed as absolute values and percentages and numerical variables in means ± standar deviation. Obesity: body mass index >30. Noncoronary vascular disease includes peripheral or cerebrovascular disease.

Table 2
Analytical Profile of Patients Included in the Score and Validation Cohorts

	Score cohort, 2005-2006 (n = 312)	Validation cohort, 2008 (n = 108)	*P* value
UDB, no. (%)	53 (17)	24 (22.2)	.3
Prediabetes, no. (%)	144 (46.2)	38 (35.2)	.07
Normoglycemia, no. (%)	115 (36.8)	46 (42.5)	.23
Biochemistry			
A_{1C} (NGSP) (%)	5.5 ± 0.5	5.6 ± 0.5	.02
LDL-cholesterol (mg/dl)	88.9 ± 38.7	96.7 ± 46.4	.02
Triglycerides (mg/dl)	106.3 ± 70.8	106.3 ± 88.6	.45

A_{1C} (NGSP), glycated hemoglobin measured by National Glycohemoglobin Standardization Program method; LDL, low density lipoprotein; UDB, unknown diabetes.
Prediabetes, includes impaired fasting glucose and impaired glucose tolerance.
Categorical variables expressed as absolute values and percentages and numerical variables in means ± standar deviation.

Table 3
Multivariate Analysis for Predicting the Risk of Unknown Diabetes Diagnosed by Oral Glucose Tolerance Test

	P value	OR	95% CI	Score points
FPG > 100 mg/dl	<.001	4.74	2.4-9.5	5
Age > 65 years	.015	2.85	1.2-5.2	3
Noncoronary vascular disease	.018	2.65	1.2-5.9	3
A_{1C} (NGSP) > 6.1%	.009	5.8	1.5-21.7	6
LVEF <45%	.04	2.7	1.03-7	3

A_{1C} (NGSP), glycated hemoglobin measured by National Glycohemoglobin Standardization Program method; CI, confidence interval; FPG, fasting plasma glucose; LVEF, left ventricle ejection fraction; OR, odds ratio.
Noncoronary vascular disease includes peripheral or cerebrovascular disease.
All variables were analyzed as categorical variables. A score is assigned to each according to its odds ratio.

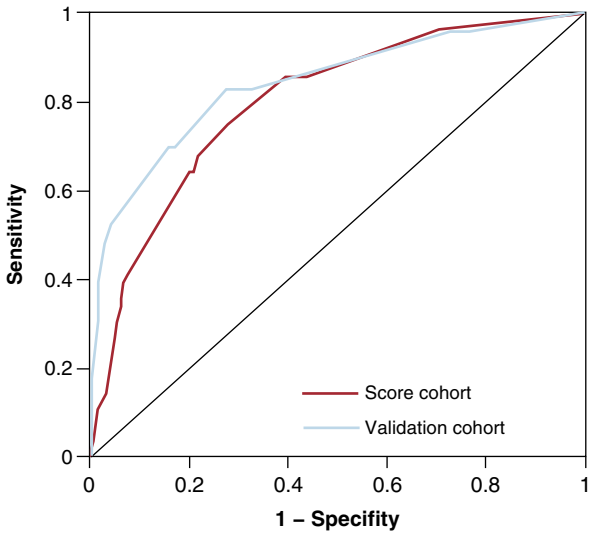

Figure 2. ROC curves of the models for determining the unknown diabetes risk score for the score cohort (AUC 0.8) and validation cohort (AUC 0.84). An absence of differences in ROC behavior curves for the cohort of the score against the validation cohort is observed (*P* = .49). AUC, area under curve; ROC, *receiver operating characteristic*.

analytical variables is useful to delimit a high risk population where the OGTT is more effective.

In total, 79 patients with UDB were identified. Diagnosis was achieved by OGTT in 53 patients (67.1%), by FPG in 20 (25.3%), and by A_{1C} in 6 (7.6%). Thus, if we apply a systematic UDB screening to the coronary population by resorting only to FPG and A_{1C}, we will lose the vast majority of patients who would have been diagnosed with OGTT. Adding A_{1C} to FPG does not achieve a significant increase in the number of diagnoses.

Why did we focus on UDB diagnosis instead of both UDB and prediabetes diagnosis? A prediabetes diagnosis will not modify secondary prevention significantly, since the change in lifestyle is already included in the recommendations for these patients[16] and moreover, its prognostic value is not confirmed.[17] On the other hand, and according to the European guidelines,[8] a UDB diagnosis would require the prescription of metformin and ACE inhibitors, substantially modifying our objectives for blood pressure control and LDL cholesterol. Furthermore, UDB has already proven its prognostic impact at 1 year,[6] and there are data to suggest that if these patients started an antidiabetic treatment it could make a difference in the short term.[7]

The OGTT has been considered the best early detection method for abnormal glucose regulation processes, especially UDB.[8] In this sense, the work by Tabak et al.[18] illustrates, in a very academic manner, how postprandial glycemia gets altered several years before FPG in a series of patients who eventually became diabetics. In the general population, OGTT doubles the number of diabetes diagnoses vs FPG (3.5% vs 7.3%)[19] whereas in the coronary population this difference may increase 5-fold (5.3% vs 26.9%).[5] However, despite its obvious usefulness, OGTT is not yet a commonly used tool to screen UDB in the coronary population. This is due to multiple factors, already discussed. The potential added value of A_{1C} in the diagnosis of UDB in this population is still unknown.

The aim of our group has been to optimize, never to question, the adequacy of OGTT so as to identify those patients solely with UDB. We have built a simple score with a 0 to 20 range of values which includes both analytical and clinical variables. Each variable in the score was weighted using the closest integer to its OR. The

Table 4
Performance of Different Models for the Screening of Unknown Diabetes by Oral Glucose Tolerance Test

	High risk, %	Sensitivity	Specificity	PPV	NPV	Youden index	AUC (95% CI)
ADA model (if FPG > 100 mg/dl)	37.9	69	69	33	91	38	0.69[a] (0.62-0.76)
WHO model (if FPG > 110 mg/dl)	13.4	42	93	13	84	35	0.67[a] (0.58-0.75)
Model Score > 6	33.7	75	73	40	93	48	0.8[a] (0.74-0.87)
Model Score > 2	69.5	96	29	25	95	25	0.8[a] (0.74-0.87)
Model Score > 11	2.9	11	99	81	14	10	0.8[a] (0.74-0.87)

ADA, American Diabetes Association; AUC, area under curve; CI, confidence interval; FPG, fasting plasma glucose; High risk, percentage of population that meets the condition; NPV, negative predictive value; PPV, positive predictive value; WHO, World Health Organization.
[a] *P* < .001.

strongest predictor variables in our score were those which reveal a scenario of abnormal glucose regulation (A_{1C} and FPG); advanced age would provide information about the greater insulin resistance present in this age group.[18] The presence of a noncoronary vascular disease may be related to the fact that up to 50% of diabetics present some kind of complication at the time of diagnosis,[20] whereas a low left ventricle ejection fraction would correspond to a greater extension of the coronary disease in these patients.[14]

If we performed OGTT only in those patients with a score >6 (31% of the total population) and added this to the UDB identified by FPG and A_{1C}, we would be effectively diagnosing 83% of the total UDB in our population. This score has been validated in a second cohort, and it has proven to be an equally useful and reproducible model. It is evident this score is not perfect, since it misses 17% of the UDB, but it would only be necessary to carry out OGTT in a third of the population at a time in which OGTT is being clearly underutilized. Moreover, if we would want to identify every case of UDB we would have only to lower the cut-off value to 2, thus reaching a negative predictive value of 95%. However, in this case the price to pay would be to perform OGTT in 64% of the population.

Our score only aims to optimize the adequacy of OGTT in the coronary population, just as other scientific groups limit its use in the general population because of the presence of risk factors.[21,22]

Limitations

The A_{1C} used when the study took place was not the standardized one (NGSP), which our laboratory adopted later on. A subsequent conversion, internationally validated, of our laboratory allowed us to calculate the equivalence.

Although clinical practice guidelines[13] recommend repeating the OGTT for UDB confirmation, in our study as in many others[4,5] it was not performed because of logistic reasons. The validation cohort is similar, although not exactly identical, to the original one. Although this fact might be considered as a limitation, we do not believe so, since not all coronary patient populations have to be equal. In our case, the original population included patients who had undergone PCI, and the validation cohort included patients admitted to our cardiology service. Thus, although some differences are undoubtedly present, the score is valid for both groups. Even though it is expected that the AUC in the validation cohort would be lower than the AUC in the score cohort, it is slightly higher but without significant differences.

Our study portrays the experience of a single center and uses relatively short series, although the results are in keeping with other published studies on larger series. It is precisely in that kind of series where this score should be validated, which for the time being should be considered as a proposal.

CONCLUSIONS

A_{1C} by itself, added systematically to the use of FPG, diagnoses only a few cases of UDB in the coronary population. However, when added to a score together with the FPG value and other clinical variables, it may help to optimize the use of OGTT. In this way, performing OGTT in only a third of the total population allows us to identify 83% of UDB patients.

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CONFLICT OF INTERESTS

None declared.

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