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Validating prediction scales of type 2 diabetes mellitus in Spain: the SPREDIA-2 population-based prospective cohort study protocol

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ABSTRACT

Introduction: The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide. When diagnosed, many patients already have organ damage or advance subclinical atherosclerosis. An early diagnosis could allow the implementation of lifestyle changes and treatment options aimed at delaying the progression of the disease and to avoid cardiovascular complications. Different scores for identifying undiagnosed diabetes have been reported, however, their performance in populations of southern Europe has not been sufficiently evaluated. The main objectives of our study are: to evaluate the screening performance and cut-off points of the main scores that identify the risk of undiagnosed T2DM and prediabetes in a Spanish population, and to develop and validate our own predictive models of undiagnosed T2DM (screening model), and future T2DM (prediction risk model) after 5-year follow-up. As a secondary objective, we will evaluate the atherosclerotic burden of the population with undiagnosed T2DM.

Methods and analysis: Population-based prospective cohort study with baseline screening, to evaluate the performance of the FINDRISC, DANISH, DESIR, ARIC and QDScore, against the gold standard tests: Fasting plasma glucose, oral glucose tolerance and/or HbA1c. The sample size will include 1352 participants between the ages of 45 and 74 years. Analysis: sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive, likelihood ratio negative and receiver operating characteristic curves and area under curve. Binary logistic regression for the first 700 individuals (derivation) and last 652 (validation) will be performed. All analyses will be calculated with their 95% CI; statistical significance will be p<0.05.

Ethics and dissemination: The study protocol has been approved by the Research Ethics Committee of the Carlos III Hospital (Madrid). The score performance and predictive model will be presented in

Strengths and limitations of this study

- Our population-based study will have greater generalisability than those studies carried out with patients attending a clinical setting. However, there are some limitations that need to be mentioned. First, a certain amount of selection bias is inevitable; older people or those who are very ill will be less prone to participate in the study. In order to avoid an unrepresentative sample of patients, a multistage sample will be collected, ensuring the study participants are representative of the general population.
- Second, a classification bias is possible due to the use of an imperfect gold standard. The oral glucose tolerance test, fasting plasma glucose and glycated haemoglobin will be chosen in order to avoid this possibility.
- Third, a confounding bias constitutes a mistake most frequently made in this type of study. In predictive models (logistic multivariable model), confounding will be assumed to be present for variables accounting for at least a 10% change of the OR. To avoid a confounding bias, the variables identified as confounding will remain in the model.

medical conferences, workshops, seminars and round table discussions. Furthermore, the predictive model will be published in a peer-reviewed medical journal to further increase the exposure of the scores.

INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide[1,2] and it is expected to continue growing

during the next decades. T2DM is a major cause of morbidity, mortality, and increasing health costs in USA[3][4] and in Europe.[5] Usually, prediabetes (impaired fasting glucose or impaired glucose tolerance) will precede the diagnosis of T2DM. It is estimated that the absolute annual incidence rates of T2DM in individuals with prediabetes vary from 5% to 10%.[6]

When patients are initially diagnosed with T2DM, they frequently have organ damage[7]; between 20% and 40% of the patients already have retinopathy,[8] 24.9% have microalbuminuria[9] and 19% have subclinical atherosclerosis.[10] This constitute a significant health problem considering the high proportion of patients with T2DM who remain asymptomatic,[11][12] and that undiagnosed T2DM has been associated with a higher risk of cardiovascular disease and mortality,[13] the leading cause of death in these patients.[14] An early diagnosis could allow the implementation of lifestyle changes and treatment options aimed at delaying the progression of the disease, and at avoiding cardiovascular complications.[15][16] For these reasons, early detection of undiagnosed T2DM is a public health priority.[17]

Early detection of T2DM can be performed measuring fasting plasma glucose (FPG) levels or with an oral glucose tolerance test (OGTT). However, the measurement of fasting or postchallenge glucose levels is an overly costly and time-consuming option to be offered to the whole population. Moreover, blood glucose levels are highly variable. For these reasons, simple scores for detecting people at risk of undiagnosed diabetes have been developed,[18] generally with good sensitivities and specificities. Most scores come from USA or from countries in northern Europe.[19] However, Mediterranean countries have a different eating pattern and a different prevalence of risk factors. It has recently been demonstrated that olive oil consumption, the main cooking oil in Spain, Italy and Greece, protects from the development of diabetes.[20] Therefore, the performance of these scores in populations from southern Europe should be evaluated.

The main objectives of our study will be to evaluate, in a Spanish population, the screening performance and cut-off points of the main scores that identify the risk of undiagnosed T2DM and prediabetes, and to develop and validate our own predictive model of undiagnosed T2DM (screening model), and future T2DM (prediction risk model) after 5 years of follow-up. As a secondary objective, we will evaluate the atherosclerotic burden of the population with undiagnosed and diagnosed T2DM.

MATERIALS AND METHODS
Study design and participants
The Screening PRE-diabetes and type 2 DIAbetes (SPREDIA-2) study is a population-based prospective cohort study with baseline screening in the region of Madrid (Spain). The study will be carried out from 1 January 2013 to 31 December 2018.

The target population will be a random sample of urban subjects living in the north-west metropolitan area of Madrid (Spain), and with healthcare coverage. Inclusion criteria will be: age between 45 and 75 years. In the reference population, there are approximately 183 000 people of this age.

In our study, potential participants, out of the overall individuals with healthcare coverage from the Spanish National Health Service, will be randomly selected by their individual health cards accessed through an electronic health records database.

The study procedure will be divided into three phases (figure 1). First, the potential participants will be sent a letter, signed by their general practitioner, explaining the objectives of the study and inviting them to participate. Second, participants will be contacted by telephone, for solving doubts, and those interested in participating will be cited for the assessment. In order to minimise the loss attributable to failure in locating the patient, up to four telephone calls will be made at different times and on different days. Pregnant women, participants with severe chronic or terminal illnesses, institutionalised participants or those chronically treated with steroids or antipsychotic drugs, will be excluded from the study. Third, participants will be attended to at the assessment.

Those participants not interested in participating will be asked to voluntarily report their sex, age and diabetes status in order to be compared with the participating population.

Procedure
Baseline screening
Participants will be scheduled in the outpatient clinic of the Hospital Carlos III after an overnight fast. On arrival, and after signing a consent form, a fasting blood analysis will be obtained for measuring the blood levels for glucose, creatinine, glycated haemoglobin (HbA1c), lipids and lipoproteins. Samples of plasma and serum will be frozen at −80°C for further analysis. Also, a whole blood sample will be obtained for DNA extraction and a urine specimen will be collected for determining microalbuminuria.

Immediately after blood sampling, all participants without a previous diagnosis of diabetes will have an OGTT with 75 g of anhydrous glucose in a total fluid volume of 300 mL. A second blood sample will be obtained 2 h later.

During the time between the taking of blood samples, patients will complete a protocolised schedule, designed in advance, to collect all the variables of the study, as follows: diabetes risk scores for predicting diabetes and a set of questionnaires will be self-administered, clinical variables and treatments will be collected by the doctors, and anthropometric parameters assessed by nurses.

Follow-up
After 5 years, the patients will be scheduled for a follow-up visit. Clinical outcomes (development of
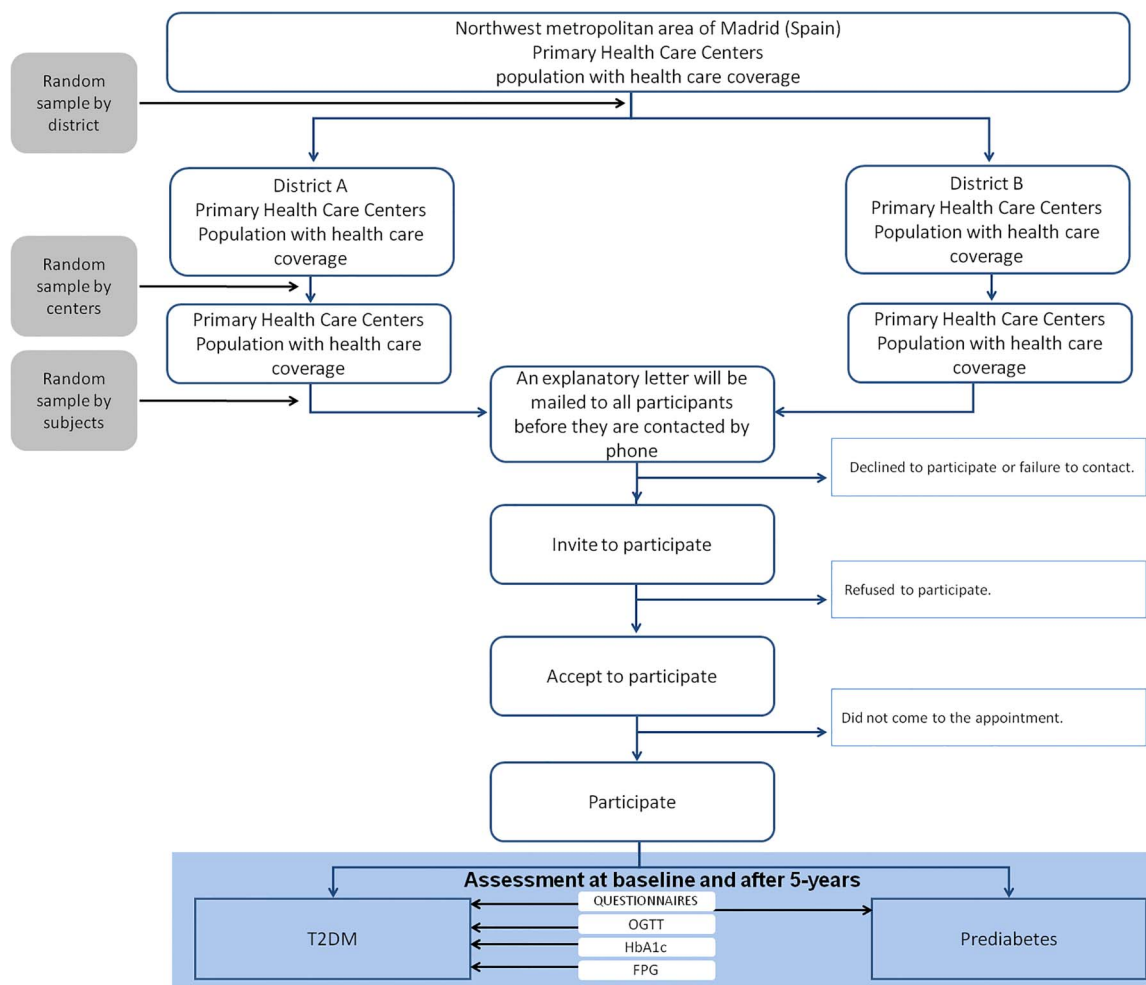
Figure 1 Study flow chart (FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

diabetes mellitus or initiation of antidiabetic agents) will be obtained from primary care electronic medical records. All participants will have a brief physical examination and a fasting blood analysis for determining glucose, creatinine, lipid parameters and HBA1c. Non-diabetic participants will have an OGTT. The vital status of patients lost to follow-up will be checked using the information provided by their general practitioners, family members and/or from a death certificate database available from the National Institute of Statistics.

Variables

The main outcome will be the diabetes status, and will be performed according to the American Diabetes Association (ADA) criteria,[21] as follows:

▶ *Prediabetes* will be defined as not having previous diabetes, but having HbA1c between 5.7% and 6.4%, or FPG between 100 and 125 mg/dL (impaired fasting glucose), or a 2 h-OGTT plasma glucose between 140 and 199 mg/dL (impaired glucose tolerance).

▶ *Undiagnosed diabetes* will be defined as not having previous diabetes, but having HbA1c ≥6.5%, or FPG ≥126 mg/dL, or 2 h OGTT plasma glucose ≥200 mg/dL.

▶ Finally, *diagnosed diabetes* will be defined as having previous diagnosis of diabetes.

Also, the following variables will be collected:

– Sociodemographic variables: date of birth, gender, nationality, ethnicity (White, Indian, Pakistani, Bangladeshi, other Asian, Black Caribbean, Black African, Chinese, other ethnic group) and educational level (no education completed, primary, secondary, university).

– Clinical variables and treatments: family history of prevalent diseases (diabetes, coronary heart disease, cerebrovascular disease), cardiovascular risk factors (smoking, hypertension, alcohol ingestion), comorbidities and current treatments. Also, hypertension will be considered if the patient has a blood pressure >140/90 mm Hg or is treated with antihypertensive drugs.

– Other clinical variables: Ankle-Brachial Index (ABI) will be determined using a portable bidirectional 8 MHz echo-Doppler and a calibrated mercury sphygmomanometer. Systolic blood pressure (SBP)

will be measured in the posterior tibial and dorsalis pedis artery of both lower limbs, and in the brachial artery of both upper limbs. The ABI value for each of the lower limbs will be determined by dividing the highest SBP obtained in each lower limb, whether posterior tibial or dorsalis pedis, by the highest SBP obtained in either of the upper limbs. Also, an eco-Doppler of both carotids will be performed with a 7.5 MHz probe (Sonosite Micromaxx Ultrasound, Sonosite Inc, Bothell, Washington, USA). Patients will lay in the supine position with the neck rotated to the side opposite that of the examination. One centimetre images will be obtained from the distal wall of the common carotid artery proximal to the bifurcation, in three different angles views. Intima-media thickness (IMT) will be obtained with automated software (Sonosite, Sonocalc IMT Software, Sonosite Inc, Bothell, Washington, USA), and the maximal region and the overall mean IMT values for each of the six segments analysed (3 angles in 2 territories), will be calculated. IMT values for the three different projections and for right and left carotid arteries will be averaged to obtain the maximum-common carotid artery (CCA)-IMT and the mean-CCA-IMT. Carotid plaques will be defined as a local thickening of the intima >1 mm or a thickening of >50% of the surrounding IMT value. Carotid stenosis will be determined according to lumen narrowing and flow velocities.

– Anthropometric parameters: All participants will have a physical examination with the determination of height, weight and waist circumference (midway between lowest rib and the iliac crest). Blood pressure will be measured three times after the participant has been seated for 5 min, and the result will be the mean of the last 2 measurements.

– Laboratory measurements: blood levels of glucose, creatinine, HbA1c, lipids and lipoproteins. Samples of plasma and serum will be frozen at −80°C for further analysis. Also, a whole blood sample will be obtained for DNA extraction, and a urine specimen will be collected for determining microalbuminuria. Finally, glucose will be measured by the glucose oxidase method. Cholesterol and triglycerides will be determined by enzymatic assays. Low-density lipoprotein (LDL) cholesterol will be calculated according to the Friedewald formula (LDL cholesterol=total cholesterol (high-density lipoprotein (HDL) cholesterol +trigyceride/5)) in participants with triglycerides below 400 mg/dL. HDL cholesterol will be measured after precipitation of apoB lipoproteins. HbA1c will be measured using a high-performance liquid chromatography method.

– Participants will complete a set of questionnaires during their visit, including the following: the 14-item questionnaire assessing adherence to the Mediterranean diet,[22] a brief physical activity

questionnaire (light, moderate, vigorous and sport level physical activity), the Patient Health Questionnaire-9, (PHQ-9),[23] to assess depression, and the 12-item Short Form Health Survey (SF-12)[24] to assess health-related quality of life; and for males, a five-item version of the international index of erectile function (IIEF-5) will be included.[25] Also, participants will complete the required questions for the validation of each diabetes risk scale.

– Diabetes risk scores for predicting diabetes. Participants will complete an extensive questionnaire to collect the data necessary to classify them according to the different diabetes risk scores for predicting diabetes: FINDRISC,[26] DANISH,[27] DESIR,[28] ARIC[29] and QDScore[30]

○ The FINDRISC[31] is an eight-item score (0–26 points) that collects data about age, sex, weight and height, waist circumference, use of concomitant medication (blood pressure), history of blood glucose disorders, physical activity and daily consumption of vegetables, fruits or berries. A higher score indicates a higher risk. The score was developed in Finland (2003). To date, external validation has been performed in 11 countries: Germany,[32–34] the UK,[18] Bulgaria,[35] China,[36] Kuwait,[37] Taiwan,[38] the Philippines,[39] Italy,[40] Spain,[41] the USA[42] and Greece[43] (table 1). This score has also been used as a screening tool to predict the risk of incident diabetes in prospective studies (table 2).

○ The DANISH[27] score includes the following variables: age, sex, body mass index (BMI), known hypertension ("Have you ever been told that you have or have had hypertension?"), physical activity at leisure time (sedentary, moderate, active and competitive sport) and family history of diabetes. The study was conducted in Denmark (2004). To date, external validation has been performed in Australia,[49] the UK[18] and Taiwan.[38]

○ The DESIR[28] score includes the following variables: sex, waist circumference, hypertension (≥140/90 mm Hg) or hypertension treatment, family history of diabetes and smoking. The score was developed in France (2008).

○ The ARIC[29] score includes the following variables: age, parental history of diabetes, ethnicity (Black), SBP, waist circumference and height. The score was elaborated in USA (2005).

○ The QDScore[30] (http://www.qdscore.org/) includes the following variables: ethnicity (9 ethnicities: White, Indian, Pakistani, Bangladeshi, other Asian, Black Caribbean, Black African, Chinese, other ethnic group), age, BMI, smoking status (non smoker; ex-smoker; light smoker: <10; moderate smoker: 10–19; heavy smoker: >19), history of diabetes in a first degree relative, cardiovascular

Table 1 Comparative data from cross-sectional studies that have used the FINDRISC score to evaluate the prevalence of undiagnosed T2DM

Study	Country	Age	Sample	N	Se	Sp	NPV	Cut-off	AUC	Gold standard
Lindström and Tuomilehto [26]	Finland	35–64	Without antidiabetic drug	4746	77	66	99	≥9	0.80	OGTT and/or FPG*
Franciosi et al [40]	Italy	55–75	No CV events & ≥1 CVRF	1377	86	41	93	≥9	0.72	OGTT and/or FPG*
Saaristo (2005) [44]	Finland	45–74	Population random sample	2966	66 (men) 70 (women)	69 (men) 61 (women)	94 (men) 96 (women)	≥11	0.72 (men) 0.73 (women)	OGTT and/or FPG*
Rathmann et al [32]	Germany	55–74	Population-based study	1353	82	43	96	≥9	0.65	OGTT and/or FPG*
Bergmann et al [33]†	Germany	41–79	3 DRF	526	70	63		≥9	0.75	OGTT and/or FPG*
Korhonen (2009) [45]	Finland	45–70	≥1 DRF	1469	62	59		≥12		OGTT‡
Li et al [34]	Germany	14–93	Family MS	771	70.1	78.6	96	≥14	0.81	OGTT and/or FPG*
Lin et al [38]	Taiwan	≥18	Population-based study	2759	67	67			0.73	FPG*
Witte et al [18]	The UK	35–55	Civil servants	6990	40	82		≥9	0.67	OGTT and/or FPG*
Al Khalaf et al [37]	Kuwait	>19	Civil servants	460	83	70		≥9		FPG¶
Makrilakis et al [43]	Greece	35–75	High-risk individuals	869	81	60	96	≥15	0.72	OGTT and/or FPG*
Tankova et al [35]	Bulgaria	22–78	≥1 DRF	2169	78	62		≥12	0.71	OGTT and/or FPG‡
Soriguer et al [41]	Spain	>30	Population-based study	1051				≥9	0.74	OGTT and/or FPG*
Ku and Kegelsl [39]	The Philippines	20–92	Population-based study	1752	62	74	96	≥9	0.74	FPG/FPG or OGTT**
Costa (2013) [46]	Spain	45–75	Population random sample	1712	76	52	95	≥14	0.67 (men) 0.76 (women)	OGTT
Zhang et al [42]	USA	≥20	Population-based study	20 633	75 (men) 72 (women)	63 (men) 69 (women)	98 (men) 99 (women)	10 (men) 12 (women)	0.75	FPG, OGTT and/or HbA1c

*WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 1999.
†German version of FINDRISC (6 variables).
‡WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006.
¶ADA. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. 2003.
**First step: FPG or casual blood glucose; second step: If FPG ≥126 mg/dL or casual blood glucose ≥200 mg/dL, the diagnosis was confirmed with new FPG (≥126 mg/dL) or OGTT (≥200 mg/dL).
ADA, American Diabetes Association; AUC, area under curve; CV, cardiovascular; CVRF, CV risk factors; DRF, diabetic risk factors; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MS, metabolic syndrome; NPV, negative predictive value; OGTT, oral glucose tolerance test; Se, sensitivity; Sp, specificity; T2DM, type 2 diabetes mellitus.

Table 2 Follow-up studies to develop and validate the FINDRISC questionnaire for predicting risk of incident diabetes mellitus

Study	Country	Age	Sample characteristics	N	Se	Sp	NPV	Hosmer-Lemeshow	AUC	Gold standard
Alssema (2008)[47]*	The Netherlands	28–75	From Hoorn, and PREVEND studies	2439; 3345	84 (cut-off≥7); 52 (cut-off≥10)	42 (cut-off≥7); 76 (cut-off≥10)	94 (cut-off≥7); 91 (cut-off≥10)	–	0.71	OGTT, FPG
Alssema (2011)[48]†	The Netherlands, Denmark, Sweden, The UK, Australia, Mauritius	46–60	Data pooling from DETECT-2 project	18 301	76	63	–	p=0.27	0.77	OGTT and self reported
Lindström and Tuomilehto [26]	Finland	45–64	Random sample from National Population Register in 1987 and 1992	4746; 4615	78 (cut-off≥9)	77 (cut-off≥9)	0.99	–	0.85	OGTT, FPG, diabetes drugs
Bergmann et al[33]‡	Germany	41–79	Participants with increased risk of T2DM	526	73 (cut-off≥9)	67 (cut-off≥9)	–	–	0.77	OGTT
Soriguer et al[41] [46]	Spain	18–65	66.9% under 45 years old	714	–	–	0.96 (cut-off≥9)	–	0.75	OGTT

*Modified FINDRISC (age, BMI, waist circumference, use of antihypertensive drugs, parental history of diabetes, family history of diabetes in first degree relative).
†Modified FINDRISC (age, BMI, waist circumference, use of antihypertensive drugs, history of gestational diabetes, sex, smoking, family history of diabetes).
‡Modified FINDRISC (only 6 variables. diet and physical activity were excluded). Sensitivity and specificity calculated from population without intervention programme.
AUC, area under curve; BMI body mass index; FPG, fasting plasma glucose; NPV, negative predictive value; OGTT, oral glucose tolerance test; Se, sensitivity; Sp, specificity; T2DM, type 2 diabetes mellitus.

disease (heart attack, angina, stroke or transient ischaemic attack), treated hypertension and treatment with steroids. The study was conducted in the UK (2009). To date, external validation has been performed in the UK.[50]

Sample size

For the main objective, the following assumptions have been accepted: an α error of 0.05, a precision rate of 9% in a bilateral contrast, for an estimated sensitivity rate of 81%[26] and an estimated prevalence of undiagnosed DM of 6%[51]; the overall sample size required 1217 participants. Given these assumptions, and expecting that 10% of individuals do not meet the inclusion criteria, the final sample size will require 1352 participants.

Data analysis plan

Descriptive statistical analysis of each variable will be carried out, summarising the quantitative variables (mean and SD, or median and the IQR for asymmetric distributions) and the qualitative variables (relative frequency). Participants not willing to participate in the study will be compared with participants, according to sex, age and known diabetes status.

For the first main objective, a 2×2 contingence table with T2DM (Yes/No) according to OGTT, FPG or HbA1c (Yes/No) and a FINDRISC score with a cut-off point of 8 (<8), will be created. This same process will be repeated for cut-off points from 9 to 16. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios will be calculated for each table. Subsequently, the process will be repeated with the rest of the predictive risk scale scores: ARIC, QDScore, DANISH, DESIR. Finally, 2×2 contingency tables will be produced for each scale with the variable prediabetes (Yes/No).

The most appropriate cut-off point on the receiver operating characteristic (ROC) curve will be calculated in order to combine the best sensitivity with the least amount of false positives (1-specificity). When comparing scores, the score with a better areas under curve (AUC) is preferred due to its better diagnostic power. The Hanley and McNeil test to contrast hypotheses will be used. Finally, we will develop and validate an own predictive model using a binary logistic regression analysis with the backward stepwise method, with the dependent variable being the presence or not of undiagnosed DM (Yes/No). Following this, independent variables with a significance of <0.20 in the univariate analysis will be introduced into the model. A split-sample technique will be used to test a prediction rule; so, 50% of the sample will be used for the development of the model, and the other 50% will be used for the validation. Regression coefficients from the predictive model will be transformed into a score by rounding up their value to the nearest whole number and multiplying by 10.

These scores will enable different cut-off points within the predictive model to be established. For each of these, the sensitivity, specificity, and positive and negative predictive values will be calculated. Finally, the best cut-off point on a ROC curve will be estimated. To calibrate the model, the Hosmer-Lemeshow test will be used and applied to the same working sample (internal validity), and the validation sample (generalisability). The ROC AUC measures discrimination, and the ability of the test to classify those with and without T2DM. Thus, for all the possible pairs of individuals (formed by an individual who had an event and an individual who did not), the model can predict the proportion of those who have a higher probability of having the event (in this case T2DM). An acceptable discrimination area for the model will be from 0.7.

The same methodology will be applied to develop and validate the 5 years prediction risk model of future T2DM.

All analyses will be calculated with their 95% CI; statistical significance will be set at p<0.05. Statistical processing of the data will be performed with SPSS (SPSS for windows, V.19.0; IBM Corp, Armonk, New York, USA).

Ethics and dissemination

The study protocol has been approved by the Research Ethics Committee of the Hospital Carlos III in Madrid. The study will comply with the International Guidelines for Ethical Review of Epidemiological Studies (Geneva, 1991). All patients will sign an informed consent form.

Finally, to guarantee the quality of reporting of the study, the protocol has been developed according to the STARD (Standards for Reporting of Diagnostic Accuracy) statement.[52]

The score performance and predictive model will be presented in medical conferences, workshops, seminars and round table discussions, and free copies for download will be made available on the website of the primary care administration (https://saluda.salud.madrid.org/ATENCIONPRIMARIA/Paginas/Default.aspx). Furthermore, the predictive model will be published in a peer-reviewed medical journal to further increase the exposure of the scores.

DISCUSSION

Diabetes is increasingly been diagnosed in industrialised countries, mainly as a consequence of the epidemic of obesity. Patients with diabetes have high morbidity and mortality, and are responsible for overconsumption of resources. Cardiovascular disease is the leading cause of death in this population.

Early diagnosis of diabetes, before the onset of clinical symptoms, would favour the implementation of lifestyle modifications that could retard its progression and avoid the development of atherosclerotic lesions. Moreover, the demonstration that participants with diabetes have a higher atherosclerosis burden at the time of diagnosis,

will further strength the recommendation of establishing strategies directed to early detection and treatment.

Different screening strategies have been adopted in order to detect undiagnosed T2DM. Currently, there are two basic methods, a population based and an opportunistic, or high risk, strategy.

Regarding the population based screening strategy, there are at least three possible approaches: (1) to determine blood fasting glucose—a strategy that serves to establish the existence of prediabetes or undiagnosed T2DM; (b) to estimate the long-term risk of T2DM—a strategy that ignores the actual blood sugar level and is based on predictive models and (c) to apply scores as screening tools, in order to identify high-risk populations that could benefit from a targeted screening programme, either measuring fasting or postprandial glucose levels.

The use of FPG levels as a population-level screening tool is not recommended due to the variability of its plasma levels and its low cost-effectiveness.[53] However, the cost-effectiveness improves when used in high-risk subgroups (ie, age over 45 years, history of gestational diabetes, family history of diabetes, obesity, hypertension or dyslipidaemia). Currently, there is no consensus on the selection of the optimal high-risk subgroups or on how regularly these screens should be performed. As a consequence, risk scores have been developed in order to better identify high risk participants.

The most well-known scores are those developed by the ADA,[54] the University of Maryland (http://www.healthcalculators.org/calculators/diabetes.asp), the German Institute of Human Nutrition[55] and the Finnish Diabetes Association (Finnish diabetes risk score, FINDRISC).[26] They all have certain common advantages: the variables are simple to collect; they have open access via websites; they are inexpensive and quick, and can be self-administered. All have a similar diagnostic accuracy, with equivalent AUC for ROC, compared with those that add laboratory variables.[29 56] Despite their widespread use, few studies have directly compared the performance of the different scores. Lin et al,[38] in a cross-sectional study of 2759 Taiwanese participants, evaluated the performance of different T2DM risk scores for detecting T2DM, metabolic syndrome and chronic kidney disease. Their data showed the superiority of the FINDRISC and Cambridge scores for identifying the 'risk of undiagnosed or unknown DM' compared with the ARIC, QDScore, Oman, Danish, Thai, Asian Indian, Dutch and DESIR scores.

Despite their well-known performance in some countries, there is a lack of either validated or autochthonous scores in countries of southern Europe. The development of local scores is relevant due to the different prevalence of diabetic risk factors among countries. Moreover, some alimentary habits influencing the risk of diabetes risk drastically differ among different regions. To date, in Spain, no standard score to predict the 'risk of undiagnosed T2DM' has been sufficiently evaluated. Soriguer et al,[41] in Málaga (Spain), evaluated the performance of the FINDRISC score in a sample of young individuals

(60% under 45 years), and Cabrera de León et al,[57] in Canary Islands (Spain), developed and validated a clinical prediction diabetes risk score. Both scores have external validation limitations mainly related to the lower prevalence of T2DM in younger adults,[58] and the high prevalence of obesity and T2DM in Canary Islands.[59]

In light of the above, it is pertinent to explore how valid the main T2DM risk scores (FINDRISC, ARIC, QDScore, DANISH, DESIR) are when applied to Spain. We will determine the most appropriate score to be used in a Spanish primary healthcare setting by exploring the diagnostic efficiency of the scores, the optimum cut-off point for the population studied, and the diagnostic accuracy of the scores for T2DM and metabolic syndrome. The data provided by the study will also contribute to the development of a predictive model that would serve as a valuable tool for identifying participants with a high risk of 'undiagnosed T2DM', candidates for further screening strategies to confirm the diagnosis (ie, laboratory tests: FPG, OGTT or HbA1C). This sequential approximation (step 1: prediction score and step 2: laboratory testing) will enable a more efficient use of resources, and the possibility of calculating the diabetes risk without accessing health services.

With regard to predicting risk of developing T2DM, a recent external validation study[60] considered 12 prediction scores as basic because they were grounded on variables that can be assessed non-invasively. FINDRISC, DESIR and QDScore were included, and the external validation showed that these scores performed well to identify those at high risk of future diabetes. However, the scores should probably be adapted to the local setting and corrected for the incidence of T2DM of the population in which they are to be applied.

Also, an accurate model for predicting incident T2DM in the Spanish population will identify a population subgroup that could benefit from therapeutic interventions and lifestyle modification.

Finally, several mechanisms have been suggested[61] to explain why diabetes risk scores could help to improve patient outcomes. For example, clinicians could easily identify high risk patients in the clinical setting and could offer advice related to changes in patient behaviour and lifestyle. Also, people could easily assess their own risk, which might prompt them to clinical consultation.

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