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Does the new American Diabetes Association definition for impaired fasting glucose improve its ability to predict type 2 diabetes mellitus in Spanish persons? The Asturias Study

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Abstract

In 2003, the American Diabetes Association reduced the lower limit defining impaired fasting glucose (IFG) to 100 mg/dL. The aim of this study was to analyze the impact of this change in the definition of IFG in a low-risk white population from northern Spain. The Asturias Study is a prospective, population-based survey of diabetes and cardiovascular risk factors. The baseline examination was carried out between 1998 and 1999 when 1034 individuals (age range, 30-75 years) were randomly selected to determine the prevalence of type 2 diabetes mellitus and prediabetes in the Principality of Asturias (northern Spain). In 2004 to 2005, these same subjects were invited for a follow-up examination. All participants without known diabetes underwent an oral glucose tolerance test both at baseline and follow-up. Application of the new American Diabetes Association definition resulted in 3 times more persons having IFG. The incidence rates of diabetes were 3.8, 19.5, and 58.0 per 1000 person-years in subjects with initial FPG values <100, 100 to 109, and 110 to 125 mg/dL, respectively. Inclusion of persons with an intermediate risk in the 100- to 109-mg/dL zone to the definition of IFG changed its positive predictive value, specificity, and sensitivity to predict diabetes from 36.5%, 94.5%, and 43.2% to 19.9%, 77.3%, and 75%, respectively. Receiver operating characteristics curve analysis including all the baseline fasting plasma glucose levels from 64 to 125 mg/dL depending on their ability to predict diabetes showed that the point closest to the ideal of 100% sensitivity and 100% specificity was 100 mg/dL. In conclusion, this study indicated that lowering the cutoff point for IFG optimizes its ability to predict diabetes in this Spanish population. The addition of other risk factors such as impaired glucose tolerance, hypertriglyceridemia, and overweight to IFG can stratify diabetes risk better.

1. Introduction

The category of impaired fasting glucose (IFG) was introduced in the late 1990s to define nondiabetic fasting hyperglycemia as a category analogous to impaired glucose tolerance (IGT) [1,2]. The original values for IFG were a fasting plasma glucose (FPG) concentration of 110 mg/dL (6.1 mmol/L) or greater but less than 126 mg/dL (7 mmol/L) [1,2]. In 2003, the American Diabetes Association (ADA) reduced the lower limit to 100 mg/dL (5.6 mmol/L) to improve its sensitivity to predict diabetes [3]. This decision proved controversial because it resulted in a 2- to 4-fold increase in the prevalence of IFG, creating a "prediabetes pandemic" [4]. Moreover, a position statement by the European Diabetes Epidemiology Group (EDEG), a subgroup of the European Association for the Study of Diabetes, recommends not changing the previous definition and maintaining it at 110 to 125 mg/dL [5]. This discordance between 2 of the most important societies for the study of diabetes worldwide has led to growing confusion, and prospective data to evaluate its consequences in Spanish populations are lacking. The aim of this study was to analyze the impact of changing the definition for IFG in a low-risk white population in northern Spain.

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2. Methods

The Asturias Study is a prospective, population-based survey of diabetes and cardiovascular risk factors. The baseline examination was carried out during 1998 to 1999 to determine the prevalence of type 2 diabetes mellitus and prediabetes in the Principality of Asturias, northern Spain. The population of Asturias is 1 073 761, mostly white. Approximately half the population lives in urban areas. A 2-step sampling technique was used. Fifteen basic health areas were selected at random from among the 76 in Asturias with a probability proportional to the number of health cards of users between 30 and 75 years. A computer program was then used to randomly select 125 persons in each basic health area. The final sample size selected was 1875; 87 were excluded for various reasons (type 1 diabetes mellitus, pregnancy, severe disease, hospitalization, or use of diabetogenic drugs). Another 162 were excluded because data necessary to contact them were missing. The final sample was composed of 1626 persons, of whom 1034 (63.6%) responded. The results showed that 11.3% of all participants had diabetes; 12.4%, IGT; and 7.6%, IFG.

Between November 2004 and October 2005, the original participants were invited to undertake a follow-up examination. Vital status and current residency of all individuals were obtained from their health service identification card. Of the original cohort, 42 persons had died and 19 had left Asturias before the follow-up started. Thirty other individuals were excluded. Of the remaining 943 persons, 700 participated (74.2%). The present analysis includes only those persons who did not have diabetes at baseline (n = 630).

The study was approved by the local ethics committee, and all participants gave informed consent.

2.1. Clinical examination

All examinations and analyses were performed at the patients' local health centers by an endocrinologist and a trained nurse. Information on demographic data, smoking habits, physical activity, socioeconomic position, and a family history of diabetes was obtained by questionnaire. Medical records were reviewed to investigate previous diseases or medication.

Height, weight, and body mass index (BMI) (in kilograms per square meter) were measured with the subject wearing light clothing and without shoes. Blood pressure was measured with a digital sphygmomanometer (OMROM MX3 OMRON Healthcare, Kyoto, Japan) after several minutes in a seated position; the mean of 2 measurements taken 1 to 2 minutes apart was used for analysis.

2.2. Laboratory data

All participants without known diabetes underwent an oral glucose tolerance test (OGTT) both at baseline and follow-up, with fasting and 2-hour venous samples obtained following the recommendations of the World Health Organization [2]. The samples were centrifuged in situ using a portable centrifuge. A portable refrigerator containing the samples was taken daily to the Biochemistry Laboratory of The Central Hospital of Asturias. Glucose was determined by the hexokinase enzymatic method (Hitachi 747, Roche Diagnostics, Mannheim, Germany). Diabetes was diagnosed if FPG $\geq$126 mg/dL and/or 2-hour plasma glucose (2hPG) $\geq$200 mg/dL [2] or if the participant had a clinical diagnosis of the disease and treatment was ongoing (diet, drugs). Additional laboratory measurements included total cholesterol, high-density lipoprotein cholesterol, triglycerides (colorimetric method, Hitachi 747), low-density lipoprotein cholesterol (Friedewald formula), and glycated hemoglobin (high-performance liquid chromatography, HA-8160, ARKRAY, Kyoto, Japan).

2.3. Statistical analyses

The participants were classified into 3 zones according to their baseline FPG: 110 to 126 mg/dL (original IFG definition zone), 100 to 109 mg/dL (additional IFG zone), and <100 mg/dL (normal fasting glucose [NFG] zone). Incidence rates of diabetes in each zone were calculated in rates per 1000 person-years (95% confidence intervals [CIs]). We used a multivariate logistic regression analysis to test for effect modification controlled for age, sex, BMI, 2hPG, and triglyceride levels as continuous variables. These variables were found to be independent risk factors of diabetes in a previous analysis [6]. We then evaluated the joint risk attributed to IGT, hypertriglyceridemia ($\geq$150 mg/dL), and overweight (BMI $\geq$25 kg/m^2) in each FPG category. Finally, the predictive ability of the 2 proposed thresholds for IFG was determined by receiver operating characteristics (ROC) curve analysis.

All statistical analyses were done with SPSS 12.0 (SPSS, Chicago, IL) and Epibasic 1.0 (University of Aarhus, Nordre Ringgade, Denmark). Reported P values are based on 2-sided tests with a cutoff for statistical significance of .05.

3. Results

3.1. Characteristics of subjects according to FPG category

Using the original criteria, 52 individuals had IFG; but using the new criteria, an additional 114 had IFG (giving a new total of 166 with IFG). Thus, overall, the proportion of subjects with IFG increased 3-fold using the new ADA 2003 criteria. The additional IFG zone defined a category of intermediate risk between normoglycemic individuals and the traditional 110 to 125 mg/dL for most of the metabolic risk factors (Table 1).

3.2. Progression to diabetes

There were 44 new cases of diabetes over a mean follow-up of 6.3 years (range, 5.9-6.8 years). As shown in Table 2, the additional IFG zone defined a category of

Table 1
Baseline characteristics of nondiabetic individuals according to FPG categories

	FPG			*P* value for trend
	NFG (<100 mg/dL)	Additional IFG (100-109 mg/dL)	Original IFG (110-125 mg/dL)	
n	464	114	52	–
Age (y)	50.1 ± 12.5	54.8 ± 11.4	56.7 ± 10.7	<.001
Systolic blood pressure (mm Hg)	127.3 ± 19	134.9 ± 18.9	143.6 ± 19.3	<.001
Diastolic blood pressure (mm Hg)	80.3 ± 12.5	84.4 ± 12.7	92.0 ± 14.3	<.001
BMI (kg/m^2)	26.7 ± 4.3	28.2 ± 3.9	29.8 ± 4.8	<.001
Total cholesterol (mg/dL)	225.4 ± 41.2	235.9 ± 46.6	237.8 ± 43.1	<.05
Low-density lipoprotein cholesterol (mg/dL)	147.9 ± 37.0	156.2 ± 41.3	156.1 ± 38.1	NS
High-density lipoprotein cholesterol (mg/dL)	57.6 ± 14.6	55.3 ± 13.5	54.6 ± 13.0	NS
Triglycerides (mg/dL)	104.5 ± 70.5	125.9 ± 66.1	133.0 ± 70.9	<.001
HbA_{1c} (%)	4.7 ± 0.4	4.9 ± 0.4	5.1 ± 0.4	<.001
FPG (mg/dL)	90.0 ± 6.1	104.2 ± 2.7	115.4 ± 4.6	<.001
2hPG (mg/dL)	99.1 ± 27.9	115.9 ± 36.1	131.1 ± 38.1	<.001
IGT (%)	8.2	26.3	38.5	<.001

Data are means ± SD unless otherwise indicated. HbA_{1c} indicates glycated hemoglobin; NS, not significant.

intermediate risk for the development of diabetes. The overall incidence rates of diabetes were 3.8 per 1000 person-years in the NFG zone, 19.5 per 1000 person-years in the additional IFG zone, and 58.0 per 1000 person-years in the original IFG zone. Adjustments for age, sex, and BMI only mildly attenuated the risk values. Further adjustment for 2hPG and triglyceride levels produced a greater attenuation, although the values were still highly significant. Table 3 shows the interaction between the most important risk factors for diabetes in our study and FPG. The presence of IGT, hypertriglyceridemia, or overweight increased the risk for diabetes from 2- to 4-fold in each FPG stratum. Incidence rates of diabetes were higher in individuals in the added IFG zone with IGT or overweight than in individuals in the original IFG zone without these factors.

The ROC curve analysis including all FPG from 64 to 125 mg/dL according to their ability to predict diabetes showed that the sensitivity and specificity were 43.2% and 94.4% for the original 110-mg/dL threshold and 77.3% and 75% for the 100-mg/dL threshold, which is the point closest to the ideal of 100% sensitivity and 100% specificity over the whole glycemic range (Fig. 1).

4. Discussion

Considerable concern exists over clarifying the definition of IFG because the prevalence of type 2 diabetes mellitus is increasing in Spain [7] and identification of individuals at high risk is mandatory. Evidence exists from multiple studies that IFG has similar or even higher predictive properties than IGT in terms of risk for type 2 diabetes mellitus [8-12]. However, because IGT is much more common than IFG in most populations, its sensitivity is higher [13]. The rationale of the ADA to lower the cutoff point for IFG is to improve its sensitivity and attempt to optimize its predictive abilities [3]. Sensitivity is a major factor in planning preventive strategies because it determines the proportion of those who will develop diabetes that can potentially be controlled.

In the population studied here, we found that adding the medium-risk population, those with 100 to 109 mg/dL, to the definition of IFG results in a 3-fold increase in the prevalence of the condition; but its sensitivity to predict diabetes is increased almost 2-fold, predicting 75% of the new cases of diabetes, in addition to maintaining an adequate specificity as shown by the ROC curve: the point at which FPG was nearest to both 100% sensitivity and 100% specificity was

Table 2
Six-year incidence rates and odds ratios for type 2 diabetes mellitus according to baseline FPG categories

	FPG			*P* value for trend
	NFG (<100 mg/dL)	Additional IFG (100-109 mg/dL)	Original IFG (110-125 mg/dL)	
Person-years of follow-up	2923.2	718.2	327.6	
No. of incident cases of diabetes	11	14	19	
Incidence rate/1000 person-years (95% CI)	3.8 (2.1-6.8)	19.5 (11.5-32.9)	58.0 (37-90.9)	<.001
Adjusted odds ratio (95% CI)				
Age and sex	1	5.7 (2.5-13.2)	23.3 (9.8-55.2)	<.001
Age, sex, and BMI	1	5.1 (2.2-12.1)	18.0 (7.4-43.7)	<.001
Multivariate[a]	1	3.9 (1.6-9.8)	12.1 (4.6-31.7)	<.001

[a] The multivariate logistic regression model was adjusted for age, sex, BMI, triglyceride levels, and 2hPG as continuous variables.

Table 3
Six-year incidence rates of type 2 diabetes mellitus for various risk factors stratified for FPG categories

	FPG		
	NFG (<100 mg/dL)	Additional IFG (100-109 mg/dL)	Original IFG (110-125 mg/dL)
IGT			
No	3.4 (1.7-6,4)	13.2 (6.3-27.7)	34.7 (14.0-71.5)
Yes	8.4 (2.1-33.4)	37.0 (17.7-77.7)	95.2 (54.1-167.7)
Triglyceride level (mg/dL)			
<150	2.0 (0.8-4.8)	15.0 (7.5-29.9)	44.1 (23.7-81.9)
≥150	14.7 (6.6-32.6)	32.8 (14.8-73.1)	89.3 (46.5-171.6)
BMI (kg/m^2)			
<25	1.8 (0.5-7.4)	6.9 (1.0-49.0)	15.9 (2.2-112.7)
≥25	4.9 (2.5-9.4)	22.7 (13.2-39.1)	68.0 (42.9-108.0)

Data are incidence rates in 1000 person-years (95% CI).

precisely 100 mg/dL. This is concordant with other populations studied: the point closest to 100% sensitivity/specificity has been reported to be 103 mg/dL (5.7 mmol/L) in a Dutch population [3], 97 mg/dL (5.4 mmol/L) in a Pima Indian population [3,10], 97 mg/dL (5.4 mmol/L) in a Mauritian population [3,14], 94 mg/dL (5.2 mmol/L) in a San Antonio population [3], and 92 mg/dL in a Korean population [15], all far from the 110-mg/dL limit of the original IFG, suggesting that a lower threshold could be more appropriate. Whether this is the desirable strategy is debatable. In its position statement, the EDEG states that the decision concerning where to draw a cutoff point on a continuous scale relates to the relative harm from being a false-positive compared with a false-negative and this in turn is dependent upon the treatment consequences that follow from attribution of a label [5]. However, unlike the EDEG, we believe this is the rationale for lowering the cutoff point for IFG: interventions for these individuals at risk of diabetes should be mainly through changes in lifestyle, directed toward avoiding excess weight, particularly abdominal obesity, and increasing physical activity. The negative effects derived from a possible overreaction are thus minimal or nonexistent; and in fact, these corrective lifestyle measures should be applicable to the whole population. Of course, any cutoff point is arbitrary because fasting glucose shows a continuous progressive risk across most of the glucose range; but if a threshold has to be chosen, the optimal cutoff point, at least in this population, seems to be 100 mg/dL. On the other hand, our results suggest that relying just on FPG to determine individuals at risk does not seem to be the best option. The addition of other associated risk factors such as IGT, hypertriglyceridemia, or overweight can significantly improve the stratification of risk. Indeed, an individual with FPG levels in the added IFG zone may be at higher risk of developing diabetes than an individual in the original IFG if these additional risk factors are present.

The incidence rates of diabetes in the IFG categories in our study (19.5 and 58 per 1000 persons-years in the additional and the original IFG zones) are quite similar to those reported by Nichols et al [16] in the American population (13.4 and 55.6 per 1000 persons-years, respectively). Their incidence rates of diabetes were for newly diagnosed cases of IFG, which could explain our slightly higher rates. Less is known about incidence rates of diabetes in subjects with IGT in each IFG category. We found that diabetes risk is increased more than 3-fold in persons with IGT in both the original and in the additional IFG zones, stressing the importance of performing an OGTT in these persons. It should also be remembered that most preventive studies have been carried out in subjects with IGT (most of whom had IFG, too); so in these persons, the evidence of a benefit from intervention in delaying or preventing diabetes is maximal [17-19]. Currently, the ADA recommends treatment with metformin in persons with both disorders (IFG-IGT) [20].

Another worrying issue regarding the new IFG criteria concerns the relationship between IFG and the future risk of cardiovascular disease (CVD) or death. Some individual registers have shown an increase in mortality for IFG in the 110- to 125-mg/dL zone but not in the 100- to 109- mg/dL zone [21,22]. However, data from meta-analyses do not confirm these results. Levitan et al [23] included nearly 200 000 individuals from 29 prospective studies in which the incidence of CVD or mortality was an end point. They found a linear relationship between postchallenge blood glucose levels in the nondiabetic range and CVD, whereas a possible threshold effect with fasting blood glucose level appeared to be around 100 mg/dL, supporting the ADA revised criteria for IFG.

Our study has several strengths: (1) The sample was representative of the general population of a whole region in northern Spain, including both the urban and rural population. (2) An OGTT was performed in all patients both at baseline and at follow-up. (3) Although the participation at the follow-up of the original cohort was not complete, most baseline parameters, including age, sex, BMI, triglycerides, FPG, and 2hPG, showed no differences between participants and nonparticipants, thereby minimizing any possible selection

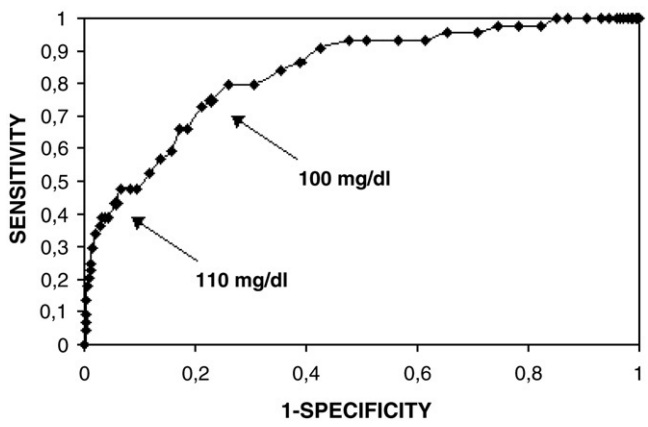

Fig. 1. The ROC curve for baseline FPG in predicting diabetes. The point closest to the ideal of 100% sensitivity and 100% specificity was 100 mg/dL.

bias. The main limitation of the study is the relatively small number of incident diabetes cases available for analysis. A larger cohort could give greater strength to our results.

In summary, this study, in agreement with the ADA recommendations, indicates that lowering the cutoff point for IFG optimizes its ability to predict diabetes in this Spanish population. The addition of other risk factors, such as IGT, hypertriglyceridemia, or overweight, to IFG can stratify diabetes risk better.

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