Using HbA_{1c} to Improve Efficacy of the American Diabetes Association Fasting Plasma Glucose Criterion in Screening for New Type 2 Diabetes in American Indians

The Strong Heart Study

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OBJECTIVE — To find an optimal critical line in the fasting plasma glucose (FPG)-HbA_{1c} plane for identifying diabetes in participants with impaired fasting glucose (IFG) and thereby improve the efficacy of using FPG alone in diabetes screening among American Indians.

RESEARCH DESIGN AND METHODS — We used FPG, 2-h postload glucose (2hPG), and HbA_{1c} measured in the 2,389 American Indians (aged 45–74 years, without diabetes treatment or prior history of diabetes) in the Strong Heart Study (SHS) baseline (second) examination. Participants were classified as having diabetes if they had either FPG ≥126 mg/dl or 2hPG ≥200 mg/dl, as having IFG if they had 110 ≤ FPG < 126 mg/dl, and as having normal fasting glucose (NFG) if they had FPG <110, according to the American Diabetes Association (ADA) definition. Logistic regression models were used for identifying diabetes (2hPG ≥200 mg/dl) in IFG participants. The areas under the receiver operating characteristic (ROC) curves generated by different logistic regression models were evaluated and compared to select the best model. A utility function based on the best model and the cost-to-benefit ratio was used to find the optimal critical line. The data from the second examination were used to study the effect of the time interval between the successive diabetes screenings on both the FPG criterion and the optimal critical line.

RESULTS — A total of 37% of all subjects with new diabetes at baseline and 55.2% of those in the second exam had 2hPG ≥200 but FPG <126. There was a very large portion of IFG participants with diabetes (19.3 and 22.9% in the baseline and second exam, respectively). Among the areas under the ROC curves, the area generated by the logistic regression model on FPG plus HbA_{1c} is the largest and is significantly larger than that based on FPG ($P = 0.0008$). For a cost-to-benefit ratio of 0.23888, the optimal critical line that has the highest utility is: $0.89 \times HbA_{1c} + 0.11 \times FPG = 17.92$. Those IFG participants whose FPG and HbA_{1c} were above or on the line were referred to take an oral glucose tolerance test (OGTT) to diagnose diabetes. The optimal critical line is lower if a successive diabetes screening will be conducted 4 years after the previous screening.

CONCLUSIONS — FPG ≥126 and 2hPG ≥200, as suggested by the ADA, are used independently to define diabetes. The FPG level is easy to obtain, and using FPG alone is suggested for diabetes screening. It is difficult to get physicians and patients to perform an OGTT to get a 2hPG level because of the many drawbacks of the OGTT, especially in those patients who already have FPG <126. It is also impractical to conduct an OGTT for everyone in a diabetes screening. Our data show that 37% of all subjects with new diabetes in the SHS baseline exam and 55.2% of those in the second exam have 2hPG ≥200 but FPG <126. These cases of diabetes cannot be detected if FPG is used alone in a diabetes screening. Therefore, although the small portion of diabetes in the NFG group (4.7% in the baseline and 6.9% in the second exam) may be ignored, those cases of diabetes among IFG participants (~20% in our data) need further consideration in a diabetes screening. It may be worthwhile for those IFG participants identified by the optimal critical line to take an OGTT. The optimal critical line and time interval between successive diabetes screenings need further study.

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Diabetes has emerged as an important medical and public health problem in the U.S. Its complications and effects on cardiovascular or other diseases as well as its burden on health care costs were reported previously (1). It is estimated that in addition to the 8 million diagnosed cases of diabetes, there are almost 8 million more people with undiagnosed type 2 diabetes in the U.S. Therefore, early detection and diagnosis of diabetes and early treatment of diabetes are very important for preventing diabetic complications and reducing both the risk

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Abbreviations: 2hPG, 2-h postload glucose; ADA, American Diabetes Association; FPG, fasting plasma glucose; 2hPG, IFG, impaired fasting glucose; INNSZ, Instituto Nacional de la Nutricion Salvador Zubiran; NFG, normal fasting glucose; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; SHS, Strong Heart Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

of other diseases and the costs of medical care for diabetic patients.

Either fasting plasma glucose (FPG) ≥126 or 2-h postload glucose (2hPG) ≥200, as suggested by the American Diabetes Association (ADA) in 1997 (2), define diabetes independently. The FPG level is easy to obtain and is suggested as the single test to use for diabetes screening. However, there are reports showing a lack of concordance between the FPG and the 2hPG criteria (3–11). Such discrepancies will reduce the efficacy of using FPG alone in diabetes screening. It is difficult to get physicians and patients to use the oral glucose tolerance test (OGTT) because of its drawbacks (12–16), especially for those patients already having an FPG <126. It is also impractical to conduct the OGTT for everyone in a diabetes screening. Thus, the participants with 2hPG ≥200 but FPG <126, especially those with diabetes among participants with impaired fasting glucose (IFG) (~20% in our data, 39% reported in a population studied by the Instituto Nacional de la Nutricion Salvador Zubiran [INNSZ] central laboratory [4]), are left undetected if FPG is used alone in diabetes screening. Therefore, an additional, simple, cost-effective, efficient, and tolerable diagnostic process for detecting these cases of diabetes would be highly desirable for diabetes screening.

Another suggested measure for clinical diagnosis or screening of diabetes is HbA_{1c}. HbA_{1c} is an integrated measure of fasting and postmeal blood glucose levels during the previous 2- to 3-month period, and it is currently used in assessing the efficacy of treatment of diabetes. Comparisons of use among HbA_{1c}, 2hPG, and FPG have been reported in the literature (17–20).

In this study, FPG, 2hPG, and HbA_{1c} data measured in American Indians in the Strong Heart Study (SHS) examinations were used. The SHS is a longitudinal and population-based study of cardiovascular disease and its risk factors in American Indians (21). The data provide a unique opportunity to examine the efficacy of using FPG alone in diabetes screening, to study possible ways to improve diabetes screening, and to address possible problems in successive diabetes screenings in American Indians.

RESEARCH DESIGN AND METHODS

— A total of 4,549 American Indians, aged 45–74 years, from 13 tribes in Arizona, Oklahoma, and South or North Dakota, participated in the SHS baseline examination (response rate >50%) (21). Among all data collected, we used the data from those 2,389 participants who were not previously diagnosed as having diabetes, did not receive insulin treatment or an oral agent for diabetes, were not on renal dialysis, did not have a kidney transplant, and had HbA_{1c}, FPG, and 2hPG measured. The same selection rules were also applied to all 3,638 participants of the SHS second examination, resulting in the use of data from 1,644 participants for this study (note that participants diagnosed as having diabetes at the baseline exam were excluded by the rules). The second exam was conducted ~4 years after the baseline exam. The details of the study design and methods have been reported by Lee et al. (21). The examinations for the study consisted of a personal interview, a physical examination, and laboratory tests. Participants were examined in the morning after at least a 12-h overnight fast. Fasting blood samples were drawn for various measurements (including glucose, lipids, and lipoproteins) after informed consent was obtained. HbA_{1c} was measured by high-pressure liquid chromatography (22). A 75-g OGGT (Glutol; Paddock Laboratory, Minneapolis, MN) was administered if the participant was not receiving insulin treatment or an oral agent for diabetes, was not on renal dialysis, had not had a kidney transplantation, and had a glucose strip test ≤225 mg/dl (One Touch glucose meter). Plasma glucose was measured 2 h after a 75-g glucose load.

Statistical analysis

A frequency table was used to show the distributions of diabetes in IFG and participants with normal fasting glucose (NFG). We let $Y_i = 1$ if the IFG participant i had 2hPG ≥200; otherwise, we let $Y_i = 0$. We let $P(Y_i = 1)$ denote the probability that IFG participant i had 2hPG ≥200. Three logistic regression models for $P(Y_i = 1)$ on FPG, HbA_{1c}, and FPG plus HbA_{1c} were fitted separately with the data from the IFG participants in the baseline exam and were used to generate receiver operating characteristic (ROC) curves for assessing the ability of the models to identify diabetes among IFG participants (SAS Logistic procedure [23]). The areas under the ROC curves were compared to find the best model by using the method proposed by DeLong et al. (24). The best model from our data was the model on FPG plus HbA_{1c}.

We let K denote a set of cutoff points, e.g., $K = \{k, k = 0 \text{ to } 1 \text{ by } 0.0001\}$; SEN($k$) denotes the sensitivity; SPE(k) denotes the specificity based on the cutoff point k and the best model (23); P denotes the prevalence of diabetes (2hPG ≥200) in IFG participants; R denotes the ratio of the costs for having an IFG participant with 2hPG <200 take an OGTT to the benefits to an IFG participant with 2hPG ≥200 being detected; and $U(k, P, R)$ denotes the utility function. The equation is as follows (25):

$$U(k, P, R) = P \times \text{SEN}(k) - (1 - P) \times [1 - \text{SPE}(k)] \times R \quad (1)$$

For an estimated P, if the ratio R has been specified, the utility can be evaluated at each cutoff point in K. The cutoff point with the highest utility, denoted as k^*, is chosen as the optimal cutoff point. Then, those IFG participants whose FPG_i and HbA_{1c_i} are above or on the following line

$$b \times \text{FPG}_i + c \times \text{HbA}_{1c_i} = Z^* \quad (2)$$

will be referred to take an OGTT as an additional test for possible diabetes, where $Z^* = \log(k^*/[1 - k^*]) - a$, and where a, b, and c are the estimated intercept, coefficient for FPG, and coefficient for HbA_{1c}, respectively, in the fitted logistic regression model on FPG plus HbA_{1c}. This line is called the optimal critical line. The details about this procedure are provided in the APPENDIX.

Table 1 — *FPG by 2hPG levels: the SHS*

	FPG (mg/dl)			
2hPG (mg/dl)	<110	110–126	>126	Total
Baseline exam				
<200	1,489	427	117	2,033
≥200	74	102	180	356
Total	1,563	529	297	2,389
Second exam				
<200	1,058	289	57	1,404
≥200	78	86	76	240
Total	1,136	375	133	1,644

RESULTS — Table 1 shows the frequencies of FPG by 2hPG for the 2,389 SHS baseline exam participants. From the table, among all 473 newly diabetic participants (either FPG ≥126 or 2hPG ≥200), 297 had FPG ≥126, which yielded a 62.8% sensitivity if FPG was used alone in diabetes screening. On the other hand, among those 356 participants with 2hPG ≥200, 176 (49.4%) had FPG <126. The 176 newly diabetic participants consisted of 37.2% of all new diabetes cases in the baseline exam. Among all participants with FPG <126, 102 (19.3%) of 529 IFG participants and 74 (4.7%) of 1,563 NFG participants had 2hPG ≥200.

The corresponding results from the 1,644 SHS second exam participants are also shown in Table 1. The results based on the data from the second exam can be treated as if the results were obtained from a successive diabetes screening conducted 4 years after the previous screening. Of all 297 newly diabetic participants, 133 of them had FPG ≥126, which yielded a 44.8% sensitivity if FPG was used alone in diabetes screening. Among all 240 participants with 2hPG ≥200, 164 (69.3%) had FPG <126. The 164 new diabetes cases comprised 55.2% of all new diabetes in the SHS second exam. Of all participants with FPG <126, 86 (22.9%) of 375 IFG participants and 78 (6.9%) of 1,133 NFG participants had 2hPG ≥200.

From the SHS baseline and second exams, ~20% of IFG participants had 2hPG ≥200. To detect these new diabetes cases, the three logistic regression models noted in the statistical analysis section were fitted. The ROC curves generated from the three models and the comparison results among areas under the ROC curves are shown in Fig. 1. Among them, the area under the ROC curve generated by the model on FPG plus HbA_{1c} is the largest, and it is significantly larger than that on FPG (0.7237567 vs. 0.640343, $P = 0.0008$) and is larger but not significantly larger than that on HbA_{1c} (0.7237567 vs. 0.7053313, $P = 0.463$). The area on HbA_{1c} is larger but not significantly larger than that on FPG ($P = 0.153$). Therefore, the model on FPG plus HbA_{1c} is the best. For the estimated prevalence P of diabetes in IFG participants (0.193 = 102/529 from Table 1) and different fixed-ratio R values, the optimal critical lines based on the utility function

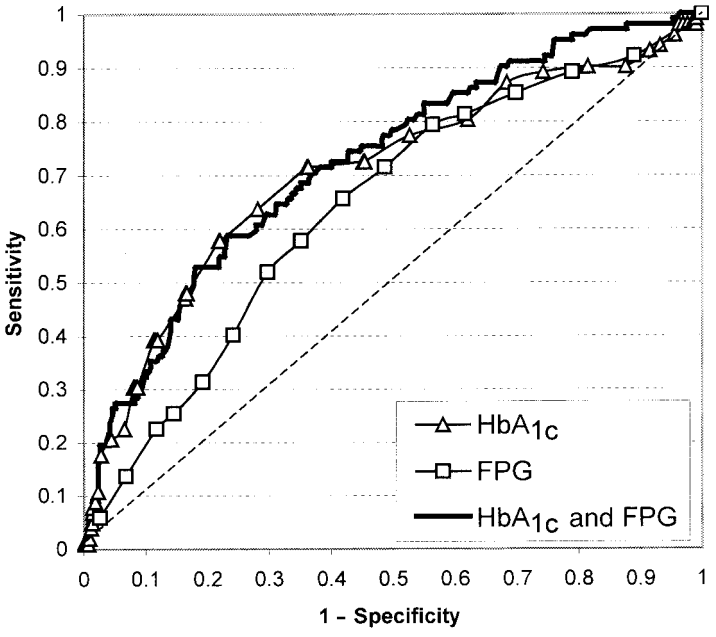

Figure 1—*The ROC curves based on the logistic regression models on FPG, HbA_{1c}, and HbA_{1c} and FPG. The areas under the respective ROC curves are denoted as the area for FPG, the area for HbA_{1c}, and the area for HbA_{1c} and FPG. They are calculated as 0.640343, 0.7053313, and 0.7237567, respectively. The results from a comparison of these areas are as follows:* P = *0.153 for the area for FPG vs. the area for HbA_{1c};* P = *0.0008 for the area for FPG vs. the area for HbA_{1c} and FPG;* P = *0.463 for the area for HbA_{1c} vs. the area for HbA_{1c} and FPG.*

(Eq. 1) and the corresponding sensitivities and specificities are listed in Table 2. From the table, if the cost-to-benefit ratio $R = P/(1 - P) = 0.23888$, the optimal critical line is

$$0.89 \times HbA_{1c} + 0.11 \times FPG = 17.92 \quad (3)$$

This critical line produced a 58.82% sensitivity with 76.82% specificity in identifying diabetes in IFG participants. The logistic regression model on FPG plus HbA_{1c} was also fitted with the data from the IFG participants in the second exam. The corresponding optimal critical lines for different R values are also listed in Table 2. For $R = P/(1 - P) = 0.2976$ (P is estimated as 86/375 from Table 1), the respective optimal critical line is

$$0.106 \times HbA_{1c} + 0.078 \times FPG = 9.43 \quad (4)$$

Both of the critical lines are shown in Fig. 2.

CONCLUSIONS — Although the cutoff point of FPG at 126 mg/dl was recommended for use as the single test for diabetes screening by the ADA in 1997, it somehow produces a low sensitivity in detecting new diabetes (62.8% in the SHS baseline and 44.8% in the second exam). A low proportion of new diabetes detected by the FPG criterion alone was also reported in older adults in the Cardiovascular Health Study (11), in a Hong Kong Chinese working population (5), in India (3), and in a population studied by the INNSZ central laboratory (4). However, the reverse was shown in Mexican-American and non-Hispanic whites in the San Antonio Heart Study (26). These varied findings may be caused by either ethnic or age-group differences or the differences from defining diabetes with the FPG and from defining diabetes with the 2hPG, as shown in the nine population-based Southern Hemisphere studies (8).

Among those newly diabetic participants in the SHS with 2hPG ≥200 but FPG <126, about half had IFG (58.0% at baseline and 52.4% in the second exam). Of the IFG participants, ~20% had 2hPG ≥200 (19.3% at baseline and 22.9% in the second exam). The high proportion having 2hPG ≥200 among IFG participants was also reported in a population studied by the INNSZ central laboratory (39% in that study) (4). Therefore,

Table 2 — *The optimal critical line for different cost-to-benefit ratio R*

R	FPG at the intercept of OCL and HbA_{1c} = 0 (mg/dl)	HbA_{1c} at the intercept of OCL and FPG = 110 (%)	HbA_{1c} at the intercept of OCL and FPG = 126 (%)	*Z**	*k**	Specificity (%)	Sensitivity (%)
SHS baseline examination (OCL: 0.89 × HbA_{1c} + 0.11 × FPG = *Z**)							
P /(1 − *P*)	162.93	6.54	4.56	17.924	0.222	76.81	58.82
0.05	153.26	5.35	3.37	16.861	0.090	18.03	97.06
0.10	154.22	5.47	3.49	16.966	0.099	23.89	95.10
0.15	157.74	5.90	3.92	17.353	0.139	44.96	83.33
0.20	160.50	6.24	4.26	17.657	0.180	61.83	71.57
0.25	162.93	6.54	4.56	17.924	0.222	76.81	58.82
0.30	164.31	6.71	4.74	18.076	0.250	81.97	52.94
0.35	164.31	6.71	4.74	18.076	0.250	81.97	52.94
0.40	164.31	6.71	4.74	18.076	0.250	81.97	52.94
0.45	164.31	6.71	4.74	18.076	0.250	81.97	52.94
0.50	169.16	7.31	5.34	18.610	0.362	95.32	26.47
1.00	170.78	7.51	5.54	18.788	0.404	97.42	19.61
SHS second examination (OCL: 0.106 × HbA_{1c} + 0.078 × FPG = *Z**)							
P /(1 − *P*)	120.31	7.61	−4.20	9.433	0.189	36.33	83.72
0.05	117.31	5.40	−6.41	9.197	0.155	9.34	98.84
0.10	117.31	5.40	−6.41	9.197	0.155	9.34	98.84
0.15	117.31	5.40	−6.41	9.197	0.155	9.34	98.84
0.20	120.31	7.61	−4.20	9.433	0.189	36.33	83.72
0.25	120.31	7.61	−4.20	9.433	0.189	36.33	83.72
0.30	120.31	7.61	−4.20	9.433	0.189	36.33	83.72
0.35	127.31	12.78	0.97	9.981	0.287	83.74	30.23
0.40	127.31	12.78	0.97	9.981	0.287	83.74	30.23
0.45	127.31	12.78	0.97	9.981	0.287	83.74	30.23
0.50	128.26	13.48	1.67	10.056	0.303	87.54	24.42
1.00	132.80	16.84	5.02	10.412	0.382	98.96	3.49

R = the costs-to-benefit ratio; *P* = the prevalence of diabetes in IFG participants, which is estimated as 0.193 and 0.229 based on the data from the baseline and second exam, respectively; k^* = the optimal cutoff point; $Z^* = \log[k^*/(1-k^*)] - a$, where *a* is the estimated intercept in the fitted logistic regression model on FPG and HbA_{1c}, and $a = -19.176$ and -10.891 based on the data from the baseline and second exam, respectively. All variables are defined in RESEARCH DESIGN AND METHODS (statistical analysis). OCL, optimal critical line.

whereas the small portion of diabetes in the NFG group (4.7% at baseline and 6.9% in the second exam) may be ignored, those diabetes cases among IFG participants need further consideration in diabetes screening. The following is a suggested procedure for diabetes screening based on our results: *1*) take measurements of FPG and HbA_{1c} (if possible) from those participants satisfying the selection rules in RESEARCH DESIGN AND METHODS, since the others should be treated individually; *2*) classify participants as having diabetes if they have FPG ≥126 and as having NFG if they have FPG <110; *3*) among participants with 110 ≤ FPG < 126, classify those participants whose FPG and HbA_{1c} are below the optimal critical line [for $R = P/(1 \times P) = 0.2388$]:

$$0.89 \times HbA_{1c} + 0.11 \times FPG = 17.92 \quad (5)$$

as having nondiabetic IFG, and refer the others to take an OGTT to get 2hPG values; and *4*) among the participants having an OGTT, classify those participants with 2hPG ≥200 as having diabetes and the others as having nondiabetic IFG.

To study the effect of the time interval between the successive diabetes screenings on the FPG criterion and the optimal critical line, we compared the data between the baseline and the second exams. The proportion of newly diabetic participants with 2hPG ≥200 but FPG <126 among all newly diabetic participants was increased significantly from 37.2% at baseline to 55.2% in the second exam ($P < 0.0001$). However, the overall proportion of newly diabetic participants with 2hPG ≥200 among all newly diabetic subjects was not increased significantly from the baseline to the second exam (from 75.3 to 80.8%, $P = 0.074$). The newly diabetic participants in the second exam had significantly lower average FPG levels than the newly diabetic participants in the baseline exam (129.5 vs. 140.2, $P < 0.001$), but this was not the case for 2hPG (234.7 vs. 239.2, $P = 0.441$). These differences may be caused by the fact that the newly diagnosed diabetic participants at the baseline exam

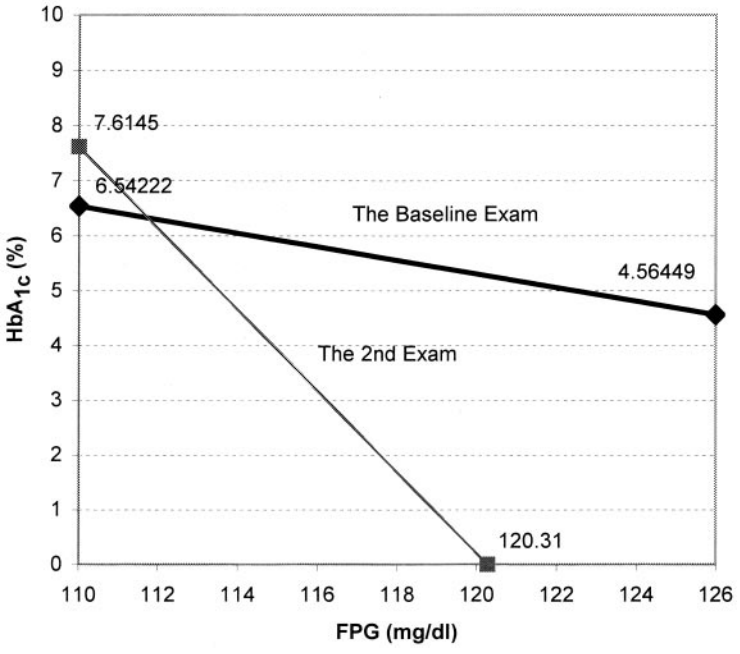

Figure 2—*The optimal critical lines for* R = P/*(1 − P) based on the data from the SHS baseline and second exams. Those IFG participants whose FPG and HbA*$_{1c}$ *are above or on the line are referred to take an OGTT for possible diabetes (2hPG ≥200 mg/dl).*

might have had diabetes for many years, whereas the newly diagnosed diabetic participants at the second exam had diabetes for at most 4 years. It may also imply that the time interval from diabetes onset to 2hPG ≥200 was less than the time interval from diabetes onset to FPG ≥126. Therefore, the sensitivity in diabetes screening by using FPG alone (62.8% at baseline and 44.8% in the second exam, $P < 0.0001$) was not as stable as that using 2hPG (75.3 and 80.8%, $P = 0.074$). Therefore, the efficacy of using FPG alone in diabetes screening is affected by the time interval between successive diabetes screenings. From the foregoing results, periodic 4-year successive diabetes screening by using FPG alone in American Indians may not be appropriate. In Fig. 2, the optimal critical line from the second exam is lower than that from the baseline exam.

CONCLUSIONS — Correct and timely diagnosis of diabetes is very important in reducing the diabetes burden. There is a discrepancy between the ADA FPG and 2hPG criteria in classifying new diabetes in American Indians. Compared with 2hPG, FPG and HbA_{1c} are much easier to obtain and are more convenient, reproducible, and reliable. It may be worth applying the proposed procedure to identify diabetes in IFG participants. The time interval between successive diabetes screenings and the adjustment for the optimal critical line need further study.

APPENDIX — Using the same notations defined in RESEARCH DESIGN AND METHODS, let p_i denote the estimate of $P(Y_i = 1)$ from the fitted logistic regression model on FPG plus HbA_{1c}. Then, from our results, we had the following (23):

$$\text{Log}[p_i/(1 - p_i)] = -19.176 + 0.116 \times \text{FPG}_i + 0.89 \times \text{HbA}_{1c_i} \quad (6)$$

For each cutoff point k in K, we classified those IFG participants with $p_i > k$ as "positive" and defined SEN(k) and SPE(k) as follows (23):

SEN(k) = (number of IFG participants with 2hPG ≥200 and $p_i \geq k$)/ (number of IFG participants with 2hPG ≥200),

$$SPE(k) = (\text{number of IFG participants with } 2hPG < 200 \text{ and } p_i < k)/(\text{number of } IFG \text{ participants with } 2hPG < 200) \quad (7)$$

The ROC curve was the plot of SEN(k) against 1 − SPE(k) for k in K (23). For $P = 0.193$ and $R = P/(1 - P) = 0.2388$, we had the optimal cutoff point $k^* = 0.222$ (Table 2). If this k^* is used, those IFG participants with $P_i \geq 0.222$, or, equivalently, from Eq. 2, with

$$0.11 \times \text{FPG}_i + 0.89 \times \text{HbA}_{1c_i} \geq \log(0.222/[1 - 0.222]) + 19.176 \quad (8)$$

will be classified as "positive" and should be referred to take an OGTT as an additional test for possible diabetes. In other words, the referred IFG participants are those IFG participants whose FPG_i and HbA_{1c_i} are above or on the following line:

$$0.11 \times \text{FPG}_i + 0.89 \times \text{HbA}_{1c_i} = 17.92 \quad (9)$$

where $17.92 = \log[0.222/(1 - 0.222)] + 19.176$.

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