HbA1c in the prediction of type 2 diabetes compared with fasting and 2-h post-challenge plasma glucose: The Asturias study (1998–2005)

S. Valdés, P. Botas, E. Delgado, F. Álvarez, F. Díaz-Cadórniga

Endocrinology and Nutrition, Hospital Universitario Central de Asturias, Oviedo, Spain
Endocrinology and Nutrition, Hospital Universitario Carlos Haya (Fundación IMABIS), Plaza del Hospital Civil, 29009 Malaga, Spain
Ciber de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Malaga, Spain
Medicine, Hospital San Agustín, Avilés, Spain
Clinical Biochemistry, Hospital Central de Asturias, Oviedo, Spain

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Abstract

Aim. – Fasting plasma glucose (FPG) and the 2-h post-challenge plasma glucose (2hPG) are commonly used to identify those at risk of type 2 diabetes. However, the role of HbA1c in this prediction has still not been ascertained.

Methods. – The Asturias study is a prospective population-based survey of diabetes and cardiovascular risk factors. Baseline examination, carried out during 1998–1999, involved 1034 individuals, aged 30–75 years, randomly selected to determine the prevalence of type 2 diabetes and prediabetes in the principality of Asturias (northern Spain). In 2004–2005, these same subjects were invited to a follow-up examination, and 700 participated. The present study includes only those who did not have diabetes at baseline. All participants with no known diabetes underwent an OGTT. Baseline HbA1c levels were measured by HPLC.

Results. – Diabetes had developed in 44 participants at the time of follow-up. Quartiles of baseline HbA1c values were 3.4–4.8 (Q1), 4.9–5.1 (Q2), 5.2–5.4 (Q3) and 5.5–6.9 (Q4), and the incidence rates of diabetes by quartiles were 1.0 (0.1–7.1), 4.0 (1.5–10.7), 7.9 (4.0–15.9) and 32.6 (22.9–46.4) cases/1000 person-years, respectively. ROC curve analysis comparing HbA1c, FPG and 2hPG in the prediction of diabetes showed areas under the curve (ROC–AUC) of 0.80 (0.74–0.86), 0.83 (0.77–0.90) and 0.79 (0.72–0.87), respectively. The combination of FPG and HbA1c had the best predictive performance with an ROC–AUC of 0.88 (0.82–0.93).

Conclusion. – Our study indicates that HbA1c is strongly predictive of new-onset diabetes in this northern Spanish population, and was similar to FPG and 2hPG in predictive capability. Also, the combined measurement of FPG and HbA1c improved their individual predictive performance.

Keywords: Type 2 diabetes; Epidemiology; HbA1c; Fasting blood glucose; OGTT; Predictive value; Asturias study

Résumé


Objectif. – La glycémie à jeun (GAJ) et l’hyperglycémie provoquée orale (HGPO) sont habituellement utilisées pour identifier les sujets à risque de développer un diabète de type 2 (DT2). La valeur de l’hémoglobine glyquée (HbA1c) dans cette prédiction n’est pas entièrement déterminée.

Abbreviations: FPG, fasting plasma glucose; 2hPG, 2-h post-challenge plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ROC, receiver operating characteristic; AUC, area under the curve; OGTT, oral glucose tolerance test; BMI, body mass index; WHO, World Health Organization; HPLC, high-performance liquid chromatography; JDS/JSCC, Japan Diabetes Society/Japan Society of Clinical Chemistry; DCCT/NGSP, Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CI, confidence intervals; SD, standard deviation; DESIR, Data from the Epidemiological Study on the Insulin Resistance Syndrome.

* Corresponding author. Tel.: +34 951030343; fax: +34 952286704.
E-mail address: sergio.valdes@hotmail.es (S. Valdés).

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Résultats. – Un DT2 est apparu chez 44 sujets au cours du suivi. Les quartiles de l’HbA1c à l’inclusion étaient de 3,4–4,8 (Q1), 4,9–5,1 (Q2), 5,2–5,4 (Q3) et de 5,5–6,9 (Q4). L’incidence du DT2 de Q1 à Q4 était respectivement de 1,0 (0,1–7,1), 4,0 (1,5–10,7), 7,9 (4,0–15,9) et 32,6 (22,9–46,4) cas pour 1000 sujets-années. L’analyse des courbes ROC comparant la valeur prédictive de l’apparition d’un DT2 de l’HbA1c, de la GAJ et de l’HGPO a mis en évidence des aires sous la courbe (co-AUC) respectivement de 0,80 (0,74–0,86), 0,83 (0,77–0,90) et de 0,79 (0,72–0,87). La combinaison de la GAJ et de l’HbA1c avait la meilleure valeur prédictive de l’apparition d’un DT2 : co-AUC 0,88 (0,82–0,93).

Conclusions. – Cette étude indique que l’HbA1c possède une valeur prédictive élevée de l’apparition d’un DT2 dans cette population, avec une capacité similaire à celle de la GAJ et de l’HGPO. La combinaison de la GAJ et de l’HbA1c améliore la performance de chaque indicateur pris isolément.

Mots-clés : Épidémiologie ; Diabète de type 2 ; Glycémie à jeun ; HGPO ; HbA1c ; Valeur prédictive ; Étude prospective ; Étude des Asturies

1. Introduction

FPG and 2hPG are commonly used to identify those at risk of type 2 diabetes. However, the role of HbA1c in such a prediction has yet to be ascertained. Measurement of HbA1c may afford certain advantages, as it has good correlation with both fasting glucose and glucose levels after an OGTT [1,2] and, thus, may serve as a measure of the average glycaemia over the preceding 8–12 weeks [3]. Measurement of HbA1c also has greater reproducibility [4] and a lower coefficient of variation [5] than do blood glucose measurements and, unlike the marked lability of glucose at ambient temperatures, HbA1c levels remain relatively stable after extraction [6]. In addition, measurement of HbA1c may be more convenient for the patient, as it can be obtained at any time and requires no fasting or testing (OGTT).

The recent introduction of a new technique to calibrate all instruments designed to measure HbA1c, thereby promoting standardization worldwide [7], may further encourage its use for the prediction of diabetes. Indeed, a recent report by an international expert committee recommended using the HbA1c for the diagnosis of diabetes and identification of high-risk individuals [8].

Nevertheless, despite these advantages, relatively few studies have examined the use of HbA1c for the prediction of diabetes [9–15], and only two involved European populations [12,13]. Furthermore, in most of these previous studies, cases of diabetes were ascertained solely by FPG (no OGTT), making direct comparisons among the predictive abilities of FPG, 2hPG and HbA1c and their combinations impossible to perform [11,13–15]. For this reason, the aim of the present study was to assess the role of HbA1c in the prediction of type 2 diabetes in a low-risk Caucasian population from northern Spain, and to compare its predictive characteristics with those of glucose measurements after an overnight fast and after an OGTT.

2. Patients and methods

The Asturias study is a prospective population-based survey of diabetes and cardiovascular risk factors [16]. Baseline examination was carried out during 1998–1999 to determine the prevalence of type 2 diabetes and prediabetes in the principalcity of Asturias in northern Spain. The population of Asturias is 1,073,761 and mostly Caucasian, and approximately half the population lives in urban areas. A two-step sampling technique was used, in which 15 basic health areas were selected at random from among the 76 in Asturias, with a probability proportional to the number of health-card users aged 30–75 years. A computer programme was then used to randomly select 125 individuals in each basic health area. The final selected sample size was 1875; 87 subjects were excluded for a variety of reasons (such as type 1 diabetes, pregnancy, severe disease, hospitalization and use of diabetogenic drugs). Another 162 individuals were excluded because necessary contact data were missing. The final sample comprised 1626 individuals, of whom 1034 (63.6%) responded. The results showed that 11.3% of all participants had diabetes, 8.9% had isolated IGT, 4.1% had isolated IFG and 3.5% had combined IFG–IGT.

Between November 2004 and October 2005, the original participants were invited to participate in a follow-up examination. Vital status and current residency of all these individuals were obtained from their health-service identification cards. Of the original cohort, 42 had died and 19 had left Asturias by the time the follow-up began. Another 30 were excluded because of pregnancy, severe disease, hospitalization or use of diabetogenic drugs. Of the remaining 943 individuals, 700 participated (74.2%) in the follow-up. The present study included only those who did not have diabetes at baseline (n = 630). The study was approved by the local ethics committee, and all participants gave their informed consent.

2.1. Clinical examination

All examinations and analyses were performed at the patients’ local health centres by an endocrinologist and a trained nurse. Information on demographic data, smoking habits, physical activity and socioeconomic position, and a family history of diabetes, were obtained by questionnaire. Medical records were reviewed to investigate previous diseases and medications. Height, weight and BMI (in kg/m²), were measured with the subjects wearing light clothing and no shoes. Blood pressure
was measured with a digital sphygmomanometer (OMROM MX3) after several minutes in a seated position; the mean of two measurements taken 1–2 min apart was used in the analyses.

2.2. Laboratory data

All participants with no known diabetes underwent an OGTT at baseline and at the time of follow-up; the fasting and 2-h venous samples were obtained according to the recommendations of the WHO [17]. 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).

Diabetes was diagnosed if FPG was ≥ 126 mg/dL and/or the 2hPG was ≥ 200 mg/dL [17], or the subject had a clinical diagnosis of the disease and treatment was ongoing (diet, drugs). Glycated hemoglobin was determined by HPLC, using a Jokoh HS-10 analyzer. The assay was performed according to the JDS/JSCC guidelines for standardization of glycohemoglobin. Intra- and inter-assay coefficients of variation for this technique were <2%. For the present report, JDS/JSCC units (NGSP/DCCT (%)) = 0.985 × JDS/JSCC % + 0.46 [18].

Additional laboratory measurements included total cholesterol, HDL cholesterol, triglycerides (colorimetric method, Hitachi 747) and LDL cholesterol (Friedewald's formula).

2.3. Statistical analyses

Participants were classified into quartiles according to their baseline HbA1c: Quartile 1, HbA1c 3.4–4.8%; Quartile 2, HbA1c 4.9–5.1%; Quartile 3, HbA1c 5.2–5.4%; and Quartile 4, HbA1c 5.5–6.9%. The incidence rates of diabetes in each quartile were calculated as rates per 1000 person-years (95% CI), and multivariate logistic-regression analysis was used to calculate the adjusted odd ratios for each group (controlled for age, gender, BMI and multivariate models). Finally, the predictive ability of HbA1c, FPG and 2hPG were compared using ROC curve analysis. All statistical analyses were done with SPSS 12.0 (SPSS, Chicago, IL, USA) and Epibasic 1.0 (University of Aarhus, Nordre Ringgade, Denmark) software, and all reported P values were based on two-sided tests with a cutoff for statistical significance of 0.05.

3. Results

3.1. Characteristics according to HbA1c quartiles

HbA1c concentrations in the study population followed a normal distribution, with a mean of 5.13% and SD of 0.46%. Table 1 shows the baseline characteristics of the study subjects according to their HbA1c quartiles during the first phase of the study. Metabolic profiles worsened progressively across all categories, as did age, systolic blood pressure, diastolic blood pressure, BMI, total cholesterol, triglycerides, and levels of FPG and 2hPG.

3.2. Progression to diabetes according to HbA1c quartiles

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 risk of type 2 diabetes was closely linked to HbA1c values. Diabetes incidence rates increased moderately from 1 to 7.9 cases per 1000 person-years across quartiles 1 to 3, and then increased dramatically to 32.6 cases per 1000 person-years in quartile 4. The last category, comprising HbA1c levels ≥ 5.5%, represented a high-risk category for the development of type 2 diabetes. Adjusted odds ratios were calculated by combining quartiles 1–3 as a reference category to avoid instability of the model. The risk of diabetes was found to be significant in logistic-regression models adjusted for age and gender and for age, gender and BMI, and also in a multivariate model including FPG and 2hPG (Table 2).

3.3. Comparison of HbA1c, FPG and 2hPG in the prediction of type 2 diabetes

Fig. 1 shows the ROC curves for FPG, 2hPG and HbA1c in the prediction of diabetes. The ROC–AUCs of these three
Table 2
Type 2 diabetes 6-year incidence rates and adjusted odds ratios according to baseline HbA1c quartiles.

<table>
<thead>
<tr>
<th>HbA1c concentrations</th>
<th>Quartile 1 (3.4–4.8%)</th>
<th>Quartile 2 (4.9–5.1%)</th>
<th>Quartile 3 (5.2–5.4%)</th>
<th>Quartile 4 (5.5–6.9%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk (n)</td>
<td>159</td>
<td>158</td>
<td>160</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Developed diabetes (n)</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Incidence rate/1000 person-years (95% CI)</td>
<td>1.0 (0.1–7.1)</td>
<td>4.0 (1.5–10.7)</td>
<td>7.9 (4.0–15.9)</td>
<td>32.6 (22.9–46.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adjusted odds ratios (95% CI)</td>
<td>Age and gender 1 8.9 (4.4–17.9) &lt; 0.001</td>
<td>Age, gender and BMI 1 7.7 (3.8–15.8) &lt; 0.001</td>
<td>Age, gender, BMI, FPG and 2hPG 1 4.2 (1.9–9.5) &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; FPG: fasting plasma glucose; 2hPG: 2-h post-challenge plasma glucose.

Fig. 1. Receiver operating characteristic (ROC) curves for baseline fasting plasma glucose (FPG), 2-h post-challenge plasma glucose (2hPG) and HbA1c in the prediction of incident diabetes.

The optimal thresholds for predicting diabetes, defined as points closest to the ideal of 100% sensitivity and 100% specificity over their whole range, were 100 mg/dL for FPG, 120 mg/dL for 2hPG and 5.5% for HbA1c. The ROC curves for combinations of these variables showed AUCs of 0.83 (0.76–0.89) for the combination of HbA1c and 2hPG, 0.84 (0.77–0.90) for the combination of FPG and 2hPG, and 0.88 (0.82–0.93) for the combination of FPG and HbA1c, with the latter combination showing the best predictive capability. The addition of 2hPG to FPG and HbA1c did not improve the model (ROC–AUC: 0.86 [0.80–0.92]).

Fig. 2 shows the combined effects of FPG and HbA1c in the prediction of diabetes. Those with FPG < 100 mg/dL and HbA1c < 5.5% were at minimal risk of diabetes, while those with FPG ≥ 100 mg/dL or HbA1c ≥ 5.5% had a low-to-moderate risk of diabetes. In contrast, those with both FPG ≥ 100 mg/dL and HbA1c ≥ 5.5% had a high risk of diabetes, with nearly one-third progressing to diabetes within six years.

4. Discussion

Our present study shows that the HbA1c may be an effective predictor of type 2 diabetes with a capability similar to FPG and the 2hPG. This, in addition to its advantages (see above), and the recent introduction of a new reference technique to calibrate and standardize HbA1c measurement around the world [7], supports the possible introduction of HbA1c values into categories of diabetes risk. According to the present study results, the high-risk category may be defined as HbA1c ≥ 5.5%, which coincides with the top quartile of HbA1c in the non-diabetic population (as measured by OGTT) as well as with the point of maximum sensitivity–specificity on the ROC curve for HbA1c in the prediction of diabetes.

The results of our study are concordant with those of previous reports in the literature. Little et al. [9] prospectively studied 257 Pima Indians with serial measurements of HbA1c and OGTT, and found that the HbA1c significantly predicted progression.
to diabetes in those with IGT. Ko et al. [10] studied the progression to diabetes in 208 Chinese individuals at high risk of diabetes, classified according to their levels of FPG and HbA1c. The combined use of both parameters proved useful for predicting diabetes. In the USA, Edelman et al. [11] studied 1253 individuals attending the department of veterans affairs medical center, and found that initial levels of HbA1c were an important predictor of diabetes in this population. In Sweden, Norberg et al. [12] studied prediction models of diabetes in 164 patients diagnosed with diabetes after a mean follow-up of 5.4 years and in 304 matched referents without diabetes. The combination of HbA1c, FPG and BMI proved effective in the screening of those at risk of diabetes. However, the addition of OGTT failed to improve the prediction of diabetes. DESIR [13] showed that HbA1c levels predicted type 2 diabetes in those with IFG, as an HbA1c of 5.9% had optimal sensitivity–specificity in these subjects. The diagnosis of diabetes, however, was based only on FPG levels (no OGTT). Two recent studies in the Japanese population have evaluated the combined use of FPG and HbA1c in the prediction of diabetes. Inoue et al. [14] studied 449 non-diabetic Japanese workers, aged 23–65 years, in whom baseline FPG levels and HbA1c were measured. High baseline HbA1c levels (≥ 5.8%) almost quadrupled the risk of diabetes in both those with high normal fasting glucose (5.55–6.09 mmol/L) and IFG (6.10–6.99 mmol/L) at baseline. Sato et al. [15] studied 6736 non-diabetic Japanese men, aged 40–55 years, and found that FPG and HbA1c were independently associated with the risk of type 2 diabetes. The model including both these factors had a greater area under the ROC curve than those including either FPG or HbA1c alone. However, these two studies failed to evaluate the role of 2hPG as, yet again, the diagnosis of diabetes was based only on FPG levels.

Thus, as with these other studies, our present study also indicates that HbA1c is a strong predictor of new-onset diabetes independently of other methods of measuring glycaemia. In addition, our study also afforded an opportunity to compare the predictive ability of HbA1c, FPG and 2hPG. ROC curve analysis showed that all three variables possessed similar predictive ability with comparable ROC–AUCs. Indeed, it is worth noting that the optimal cutoffs for predicting diabetes with these variables (defined as the points with maximum sensitivity–specificity on the ROC–AUC) were relatively low, indicating that the risk of diabetes starts with low levels of dysglycaemia within the ranges of these variables. In the case of HbA1c, a value of 5.5% could be adequate for identifying a population at increased risk of type 2 diabetes in terms of sensitivity–specificity. The possibility of making direct comparisons of the three variables also allowed evaluation of their combined predictive ability to verify previous studies showing that the combination of FPG and HbA1c offered the maximum diagnostic yield, with an AUC of 0.88 (0.82–0.93), which has an excellent predictive yield. Curiously, the combination of HbA1c and 2hPG barely increased the individual diagnostic yield of these variables, whereas the 2hPG failed to improve the model when added to the combined measurements of FPG and HbA1c. It is possible that HbA1c reflects the postprandial component of glycaemia better than the 2hPG and therefore its association with FPG may reflect glucose exposure throughout the day best.

The present findings could suggest that an OGTT is not necessary for the study of carbohydrate metabolism and, so, might instead be replaced by measurement of FPG and HbA1c. However, although this may well be the case when referring to predicting the incidence of diabetes, it is important to note that there are individuals with FPG and HbA1c levels in the non-diabetic range, but with 2hPG values ≥ 200 mg/dL (isolated post-challenge hyperglycaemia), who are at an increased risk of microangiopathy, cardiovascular disease and death [19,20], and that these cases would be missed without an OGTT.

Thus, given this premise and our present observations, the most reasonable recommendation would be to screen for diabetes using FPG. Those with levels ≥ 100 mg/dL (around 25% of the population aged > 30 years) would also have their HbA1c measured, and if this were ≥ 5.5%, then this individual would be considered to be at high risk of diabetes, and would be in need of advice and intensive preventative measures. Whenever feasible, an OGTT should also be performed in such high-risk individuals to avoid isolated post-challenge diabetes.

The present study has several strengths: (1) the sample was representative of the general population of a whole region in northern Spain, including both urban and rural populations; (2) an OGTT was performed in all patients at both baseline and follow-up and; (3) although the participation of the original cohort in the follow-up was not total, most of the baseline parameters—age, gender, BMI, triglycerides, FPG, 2hPG and HbA1c levels—showed no differences between participants and non-participants, thereby minimizing any possible selection bias. The main limitation of the present study is the relatively small number of incident diabetes cases available for analysis. Larger cohorts would have conferred greater power to our results.

In summary, our study indicates that the HbA1c is strongly predictive of new-onset diabetes in this northern Spanish population, with a predictive capacity similar to FPG and the 2hPG. Those with HbA1c levels in the top quartile (≥ 5.5%) had a high risk of diabetes, and this cutoff point was adequate in terms of sensitivity–specificity. However, the combination of FPG and HbA1c demonstrated the best predictive capability.

Conflict of interest statement

Authors report no potential conflicts of interest relevant to this article.

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