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Use of hemoglobin A1C to detect Haitian-Americans with undiagnosed Type 2 diabetes

Utilização de hemoglobina A1C no rastreamento de haitianos americanos com diabetes tipo 2 não diagnosticado

Joel C. Exebio¹, Gustavo G. Zarini¹, Joan A. Vaccaro¹,
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ABSTRACT

Objective: To evaluate the validity of hemoglobin A1C (A1C) as a diagnostic tool for type 2 diabetes and to determine the most appropriate A1C cutoff point for diagnosis in a sample of Haitian-Americans. **Subjects and methods:** Subjects (n = 128) were recruited from Miami-Dade and Broward counties, FL. Receiver operating characteristics (ROC) analysis was run in order to measure sensitivity and specificity of A1C for detecting diabetes at different cutoff points. **Results:** The area under the ROC curve was 0.86 using fasting plasma glucose ≥ 7.0 mmol/L as the gold standard. An A1C cutoff point of 6.26% had sensitivity of 80% and specificity of 74%, whereas an A1C cutoff point of 6.50% (recommended by the American Diabetes Association – ADA) had sensitivity of 73% and specificity of 89%. **Conclusions:** A1C is a reliable alternative to fasting plasma glucose in detecting diabetes in this sample of Haitian-Americans. A cutoff point of 6.26% was the optimum value to detect type 2 diabetes. *Arq Bras Endocrinol Metab.* 2012;56(7):449-55

Keywords

Type 2 diabetes; hemoglobin A1C; diagnosis; Haitians

RESUMO

Objetivo: Avaliar a validade da hemoglobina A1C (A1C) como ferramenta para o diagnóstico de diabetes tipo 2 e determinar o ponto de corte mais apropriado para a A1C no diagnóstico de uma amostra de haitianos americanos. **Sujeitos e métodos:** Os sujeitos (n = 128) foram recrutados dos condados de Miami-Dade e Broward na Flórida. A análise ROC (*Receiver operating characteristics*) foi feita de forma a medir a sensibilidade e especificidade de A1C para a detecção do diabetes em diferentes pontos de corte. **Resultados:** A área sob a curva ROC foi 0,86 usando a glicemia de jejum $\geq 7,0$ mmol/L como padrão-ouro. O ponto de corte de 6,26% para a A1C apresentou sensibilidade de 80% e especificidade de 74%, enquanto o ponto de corte de 6,50% (recomendado pela American Diabetes Association – ADA) apresentou uma sensibilidade de 73% e especificidade de 89%. **Conclusões:** A A1C foi uma alternativa confiável para a glicemia de jejum na detecção do diabetes nesta amostra de haitianos americanos. Um ponto de corte de 6,26% foi o valor ótimo para a detecção do diabetes tipo 2. *Arq Bras Endocrinol Metab.* 2012;56(7):449-55

Descritores

Diabetes tipo 2; hemoglobina A1C; diagnóstico; haitianos

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INTRODUCTION

Traditionally, the diagnosis of diabetes has been based on plasma glucose. Both fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) have been widely used for more than three decades. However, both tests are inconvenient because they require fasting

of at least 8 hours and, in the case of the OGTT, staying in the clinical facility for a long period of time.

In recent years, several studies have examined the validity of hemoglobin A1C (A1C) as a diagnostic tool for type 2 diabetes (T2D) (1-4). A1C represents a measure of mean blood glucose during the two months

before the measurement, and does not require fasting or any special preparation. In 2009, an International Expert Committee recommended the use of A1C to diagnose diabetes with a cutoff point of $\geq 6.5\%$ (5). In 2010, the American Diabetes Association (ADA) adopted this criterion (6). However, it was recognized that A1C levels may vary according to the ethnicity (7).

Data revealed that different ethnic groups show variable sensitivity and specificity for A1C. Variations may be related to genetic differences in hemoglobin concentration, glycation rates, and lifespan and number of red blood cells (8,9). When the recommended A1C cutoff point ($\geq 6.5\%$) was tested in a sample representative of the general US population, sensitivity of A1C was lower compared with FPG. In fact, with this recommended cutoff point, A1C identified 33% less cases of undiagnosed diabetes than FPG ≥ 7.0 mmol/L (10). Therefore, an argument for population-specific A1C cutoff points emerged, especially among high risk populations.

Haitians are one of those high risk populations. According to the International Diabetes Federation, the prevalence of T2D in Haiti was 7.2% for 20 to 79-year-olds in 2010 (11). Official data for Haitian-Americans (HA) are not available. A small sample ($n = 51$) collected in a Haitian community (Little Haiti) in the Miami-Dade County, FL, among Haitian immigrants estimated a 33% prevalence of diabetes (12). Since acculturation may increase obesity rates in Haitian immigrants, prevalence of T2D is likely to be higher among them compared with Haitians living in Haiti. According to the US Census Bureau, there are 548,199 Haitians living in the US, 30% of whom reside in the Miami-Dade and Broward Counties, FL, making them the second largest immigrant group (behind Cubans) in those counties (13).

The aims of this study were to evaluate the validity of A1C as a diagnostic tool for T2D, and to determine the most appropriate A1C cutoff point for T2D diagnosis in a sample of HA aged ≥ 35 years old, using the criteria of FPG ≥ 7.0 mmol/L as the cutoff point for diabetes diagnosis.

METHODS

Parent study

Participants

Our current study used male and female adults, ≥ 35 years, who were not diagnosed with diabetes in the pa-

rent, case/control study of HA with T2D ($n = 130$), and without diabetes ($n = 129$). To be considered a HA, respondents needed to self-report having two parents born in Haiti. The candidates were screened by a trained interviewer, who was familiar with Haitian culture and who spoke English and Creole. Questions concerning length of stay in the United States and place of birth were asked to candidates who qualified. The target population was recruited to achieve sufficient power (80%) to determine a medium effect (≥ 0.50) size in cardiovascular disease risk factors and to distinguish differences among 4 groups (gender and two age categories) for cases (with diabetes) and controls (without diabetes).

It was determined that 240 participants (30 participants per four groups with diabetes, $n = 120$, and without diabetes, $n = 120$) would be sufficient, based on our previous studies in other populations and by using Cohen's rule of thumb ($n = 30$ per group) (14). Since we anticipated cases of undiagnosed diabetes, the target sample size was increased to accommodate reclassification and possible missing data.

Data collection for the parent study

Recruitment was conducted by alternating between selecting potential subjects with and then without T2D. Recruitment of HA participants ($n = 259$) was from community-based sources: (a) Local diabetes educators & community health practitioners in Miami-Dade and Broward Counties (several local diabetes educators who were either former students or in close contact with the Department of Dietetics and Nutrition at Florida International University-FIU; official letters of invitation outlining the study mailed to the diabetes educators and health professionals in Miami-Dade and Broward county areas requesting their cooperation in recruiting individuals); (b) FIU faculty, staff and students (invitational flyers were distributed to all university faculty, staff and students using the university-wide e-mail system and explaining the research protocol and requesting their assistance in the study); (c) Several residential rental facilities also agreed to help in the recruitment process; (d) Advertisements (printed ads were placed in local Haitian newspapers and principal gathering places of these groups, such as churches, supermarkets, and restaurants; radio advertisement on local Creole stations was also aired).

When the recruitment target was reached (259, as explained in the "participants" section), all efforts to

recruit participants stopped. Interested participants were initially interviewed on the phone. At that moment, the study purpose was explained and the age and gender of the responders were determined. To ascertain T2D status, each participant who self-reported having diabetes was asked for age of diagnosis and initial treatment modalities. Exclusion criteria were belonging to any other ethnicity, age < 35 years old, pregnant or lactating women. If a subject was determined to be eligible, then his or her participation was requested at the Human Nutrition Laboratory at FIU. Participants were instructed to refrain from smoking, consuming any food or beverages except water, and engaging in any unusual exercise for at least eight hours prior to blood collection.

This study was approved by the Institutional Review Board at FIU. The purpose and protocol of the study were explained to the subjects, and their written consent, either in English or Creole, was obtained before the study began. Laboratory results showed that fifteen participants who reported not having diabetes were reclassified as having T2D according to FPG \geq 7.0 mmol/L. These participants were given their laboratory results and referred to their physicians.

Present study

For the present study data analysis, subjects who reported previous diagnosis of diabetes ($n = 130$) or were missing values for A1C ($n = 1$) were excluded. A total of 128 participants were included in the analysis of the data. Subjects who reported previous diagnosis of diabetes were excluded from our analysis because they were taking medication that decreased their FPG below the threshold of diagnosis, which is, in fact, the goal of the diabetes treatment.

Measures

Twenty mL of venous blood were collected from each subject after an overnight fast (at least 8 hours) by a certified phlebotomist using standard laboratory techniques. Blood samples were collected in two tubes: a Vacutainer Serum Separator Tube (SST) for analysis of glucose, and another tube containing ethylenediamine tetra-acetic acid (EDTA) to analyze A1C. After complete coagulation (30-45 minutes), SST was centrifuged at 2,500 RPM for 30 minutes. Serum was transferred from SST into labeled plastic tubes for glucose analysis. Glucose levels were measured by hexokinase

enzymatic methods. A1C percentages were measured in whole blood with close tube sampling (CTS), in duplicate ($CV < 1.7\%$), with the Roche Tina Quant Second Generation A1C (AC1-2) immunoassay method of Laboratory Corporation of America, Miami, FL (LabCorp®). The immunoassay method expresses A1C as a percent of total hemoglobin (Hb); whereas High Pressure Liquid Chromatography (HPLC) expresses A1C as a percent of total HbA. Since amino acids substitution in HbS and HbC (the most common variants of A1C) are close to the glycosylated N-terminus, it is possible to overestimate A1C; however, several studies have found comparable results using standard techniques (15-17). The system used for our assays has matched the National Glycohaemoglobin Standardization Program (NGSP) against the Hb variants and has been certified to follow The Diabetes Control and Complications Trial (DCCT) (15,16). Moreover, our immunoassay method has been validated against boronate-affinity HPLC in two groups of African American patients, one with hemoglobinopathy and another without hemoglobinopathy, and whose A1C < 7.0% (17).

Statistical analysis

Data were divided into three categories according to the current ADA classification (6): normal FPG (< 5.6 mmol/L), impaired fasting glucose (IFG) (5.6-6.9 mmol/L), and undiagnosed diabetes (≥ 7.0 mmol/L). Percentages of subjects above A1C cutoff points among the three categories were compared using bar graphs. Mean A1C for subjects with normal FPG (< 5.6 mmol/L) was computed. Sensitivity and specificity were evaluated at 1, 2, 3, and 4 standard deviations above this mean. Also, the cutoff point recommended by the ADA for diabetes diagnosis was plotted in the analysis (A1C $\geq 6.5\%$). The ADA criterion for diagnosing diabetes with FPG ≥ 7.0 mmol/L was considered the gold standard.

Receiver operating characteristics (ROC) analysis was run in order to measure sensitivity and specificity of A1C in detecting diabetes at different cutoff points, and to determine the best predictive cutoff value (18). Sensitivity is the proportion of subjects at or above the A1C cutoff point who have diabetes (FPG ≥ 7.0 mmol/L). Specificity is the proportion of individuals with A1C level below the cutoff point who do not have diabetes (FPG < 7.0 mmol/L). The ROC curve plots sensitivity *versus* 1 minus specificity at each cutoff level.

The greater the area under the curve (AUC), the better the prediction value of A1C for detecting diabetes. An AUC of 0.5 means no prediction value, whereas a value of 1.0 means perfect prediction value. Statistical analysis was run using SPSS 18.0 (Chicago).

RESULTS

Participants were all born in Haiti and reported migrating to the United States. There was no significant difference in the length of stay (less than 10 years) for those with undiagnosed diabetes compared with those without diabetes (20.0% and 30.9% respectively, $P = 0.550$). The linear correlation between A1C and FPG was highly significant ($P < 0.001$), with a correlation coefficient of 0.75. Mean A1C for participants with normal FPG, IFG and diabetes were $5.8 \pm 0.46\%$, $6.1 \pm 0.47\%$, and $7.6 \pm 1.75\%$, respectively ($P < 0.001$). No significant differences were found for age, gender, body mass index (BMI), and waist circumference among the three categories. These values were 52.5 ± 10.5 years, 51% female, 28.6 ± 4.6 kg/m², and 95.6 ± 12.1 cm for normal FPG ($n = 75$); 57.3 ± 10.6 years, 50% female, 29.3 ± 5.7 kg/m², and 96.8 ± 14.1 cm for IFG ($n = 38$); 53.2 ± 13.5 years, 40% female, 30.1 ± 5.9 kg/m², and 97.9 ± 11.6 cm for subjects with T2D ($n = 15$).

Cutoff points were determined using mean A1C for participants with normal FPG and adding 1, 2, 3, and 4 standard deviations. These points were 6.26%, 6.72%, 7.18%, and 7.64% respectively. In addition, the cutoff point recommended by the ADA (A1C $\geq 6.5\%$) was also evaluated. Figure 1 shows the percentage of the population at or above specific cutoff values. Thirty-two percent of the population had A1C levels at or above 6.26% and 18.8% had A1C levels at or above 6.50%. A total of 44.7% of subjects with IFG and 80% with undiagnosed diabetes were detected with an A1C cutoff point of 6.26%. Similarly, 18.4% of subjects with IFG and 73.3% of participants with undiagnosed diabetes were detected with an A1C cutoff point of 6.50% (recommended by the ADA).

In this specific population, A1C showed a high predictive value for detecting undiagnosed diabetes. The area under the ROC curve was 0.86 (Figure 2). In addition, an A1C cutoff point of 6.26% had sensitivity of 80% and specificity of 74%, whereas an A1C cutoff point of 6.50% had sensitivity of 73% and specificity of 89%. Sensitivity decreased as specificity increased with every increasing cutoff value (Table 1).

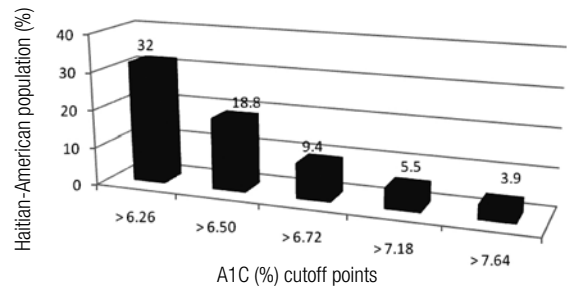


Figure 1. Percentage of Haitian-Americans aged ≥ 35 years old at different A1C cutoff points.

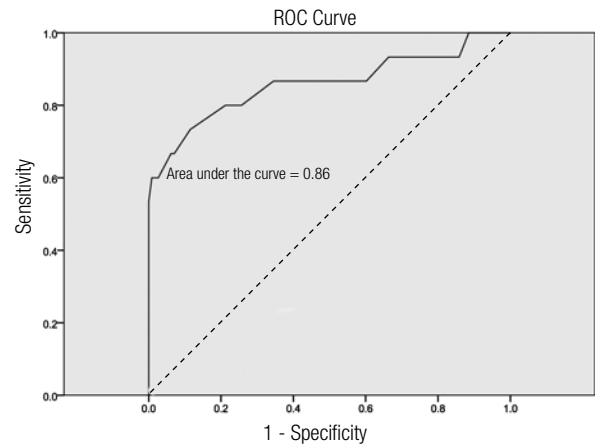


Figure 2. Continuous line: ROC curve for A1C as a diagnostic indicator for diabetes (fasting plasma glucose ≥ 7.0 mmol/L). Dotted line: Diagonal indicating area under the curve = 0.50.

Table 1. Sensitivity and specificity of A1C for detecting undiagnosed diabetes in Haitian-Americans (fasting plasma glucose ≥ 7.0 mmol/L) at increasing A1C cutoff points

A1C cutoff (%)	Sensitivity	Specificity
6.26	80	74
6.50	73	89
6.72	60	97
7.18	47	100
7.64	33	100

Data are %. Sensitivity: $100 \times TP / (TP + FN)$. Specificity: $100 \times TN / (TN + FP)$. TP: true positive (above the cutoff level for A1C and FPG ≥ 7.0 mmol/L); FN: false negative (below the cutoff level for A1C and FPG ≥ 7.0 mmol/L); TN: true negative (below the cutoff level for A1C and FPG < 7.0 mmol/L); FP: false positive (above the cutoff level for A1C and FPG < 7.0 mmol/L).

DISCUSSION

The ADA has adopted A1C as a valid diagnostic tool for diabetes on the basis that the test is now standardized, does not require fasting, has less intra-individual variability than FPG, and is not affected by stress or illness.

The recommended cutoff value for diabetes diagnosis has been set at A1C $\geq 6.5\%$ (6). In a recent study using data from the National Health and Nutrition Examination Survey (NHANES), A1C $\geq 6.5\%$ detected only 30% of the subjects with undiagnosed diabetes. In addition, 19% of subjects with undiagnosed diabetes were detected by both FPG and OGTT, but not by A1C. Similarly, 1% of the population previously diagnosed with diabetes, but who has not taken medication yet, was not detected by A1C (10). These results from a sample representative of the national US population demonstrate that the arbitrary cutoff point of 6.5% should be considered with caution.

Studies from several countries have documented that different ethnicities have different A1C values (1-4,8). High sensitivity is important for minorities, even at the expense of lower specificity, in order for cases to be discovered. In the US, the Diabetes Prevention Program has shown that African Americans and Hispanics with impaired glucose tolerance (IGT) had higher A1C values compared with non-Hispanic Whites with IGT, even after adjusting for confounding variables. This finding may be explained by other factors that are not related to glucose control such as hemoglobin glycation rate or red blood cell survival time (9).

In our sample, mean A1C for subjects with normal FPG (FPG < 5.6 mmol/L) was $5.8\% \pm 0.46\%$, which is higher compared with other populations. For instance, in data obtained from the NHANES III, mean for subjects with normal FPG was $5.17\% \pm 0.45\%$ (19). The difference is even greater if we take into consideration that, in this study, normal FPG was defined as FPG < 6.1 mmol/L, which may have increased mean A1C compared with a cutoff of FPG < 5.6 mmol/L. Means for the US population without diabetes are usually higher because they include people with normal and high FPG. However, they are still lower than that found in our sample for subjects with normal FPG. For instance, the overall mean A1C found in the NHANES for non-Hispanic Whites, non-Hispanic Blacks and Mexican Americans without diabetes were 5.3 ± 0.01 , 5.4 ± 0.01 , and $5.4 \pm 0.01\%$, respectively (20). From these results, it is inferred that even in the presence of normal FPG, A1C levels were elevated in our sample of HA compared with the US population without diabetes. Furthermore, 32% of HA without diabetes had A1C levels greater than 6.26%. In the NHANES, only 2.9% of the US population without diabetes had A1C greater than 6.1% (20). Therefore, in this particular

sample, there is a considerable proportion of HA with high A1C compared with the general US population without diabetes.

In our sample, A1C showed high predictive value in detecting undiagnosed T2D (AUC = 0.86). However, our optimal cutoff point differs from the one suggested by the ADA. Since the mean for normal subjects ± 1 SD is considered normal range in any test ($5.8 \pm 0.46\%$ in our sample), any value that is above the normal range should be considered abnormal ($> 6.26\%$ for our sample). This is further confirmed by the ROC analysis. Using an A1C cutoff point of 6.26% (1 SD above the mean for participants with normal FPG) we had 80% sensitivity and 74% specificity. Applying the A1C cutoff point of 6.5% adopted by the ADA, we had 73% sensitivity and 89% specificity. The cutoff point recommended by the ADA had lower sensitivity but higher specificity. This issue was addressed by the International Expert Committee who recommended the cutoff point (5). The argument was that specificity is more important than sensitivity because diagnosing subjects as positive when in fact, they are not, will be costly for the health system. While this may be true for the general population, in minorities like HA with a high prevalence of T2D and a high rate of poverty, the cost of complications caused by undiagnosed diabetes may offset the cost related to false positives.

This is further confirmed by studies in different high risk populations around the world that suggest either $\geq 6.1\%$ or $\geq 6.2\%$ as the optimum cutoff point for diabetes diagnosis (1-4,21-23) and by the low sensitivity found for A1C when the recommended cutoff point was applied to general US population (10). It should also be noted that 44.7% of the participants with IFG were detected by the 6.26% cutoff point, which indicates that a much lower cutoff value should be used for that purpose in this particular sample.

One reason for the lack of consensus for routine diabetes screening may be the lack of diagnostic accuracy of A1C in earlier studies. Now that technology has improved, evidence for A1C as a diagnostic tool for minorities and hard-to-reach population may be built. Once the barrier of 8-hour fasting is removed for these groups, early diagnosis and lifestyle management would have the potential to reduce diabetes-related complications. The predictive validity of A1C as a diagnostic tool (compared with FPG) was found to vary by risk factor score categories (low, moderate, and high prevalence) in a nationally representative sample (24). The

investigators found that intermediate A1C (5.5%-6.0%) could exclude diabetes for persons in the moderate, but not in the high risk groups (24). Since minorities such as HA are at high risk for diabetes, lower A1C cutoffs would increase sensitivity at the expense of lower specificity. The fact that A1C levels indicating high glycemia are positively correlated with microvascular complications (24) offsets the expense of false diagnoses.

The new diagnostic criterion will have important public health implications for high risk populations. According to our data, a considerable proportion of HA in our sample will be missed by the established cutoff point and will be left without treatment. It is imperative to have defined specific cutoff points, to explain why HA in our sample have high A1C even in the presence of normal FPG, and to examine how the rates of complications are related to A1C levels in this population.

The prevalence of undiagnosed diabetes was 11.7% (15/128) in this study. Several limitations need to be noted. Our sample may not represent the HA population in Miami-Dade County due to the small sample size and selection bias. HA who were willing to participate in a study that involved revealing social information and drawing blood may have different risk factors compared with those HA who were asked to participate, but refused. Although community leaders generally have access to hard-to-reach HA, they may have selectively approached HA with more cooperative social characteristics. Another limitation of this study was that data was taken in a single time-point. As such, temporal changes in Miami-Dade County were not taken into account.

Technical limitations existed, as well. Although FPG is the gold standard, the ADA recommends that two tests are used for accuracy, and only one measure was taken in this study. Regarding interference of hemoglobin variants, the most common variant for our population would be the HbC or the HbS trait, if HA were sampled in the "Black, non-Hispanic" category (25). The National Diabetes Clearinghouse (NIDC) estimates 8% of African Americans have the HbS trait and 2.3% have the HbC trait (26). Even though the immunoassay method used to assess A1C was validated against ion-exchange HPLC, HbS or HbC are close to the glycated N-terminus and interference resulting in higher readings cannot be completely ruled out (17). However, interference of the HbS or HbC traits are most likely to be found at the extremely high A1C values (17).

Relative contributions of fasting and postprandial hyperglycemia were found to vary across A1C quintiles in a study by Monnier and cols. (27). However, fasting hyperglycemia was critical for A1C values above 8.4%, since postprandial exposure remains stable in the three upper quintiles (27). Three categories were compared in our analysis: normal, IFG, and undiagnosed T2D using FPG. As A1C values were also from fasting blood samples, postprandial glucose levels would not be an issue in the determination of cutoff points.

A1C may be useful in detecting diabetes in community settings among HA. A positive test should be confirmed by fasting plasma glucose or a second A1C reading. However, our study with only one A1C and FPG reading mimics a common decision-making practice for diabetes diagnosis among this particular hard-to-reach population.

In our study, A1C showed a high predictive value for detecting undiagnosed diabetes in HA. A cutoff point of 6.26% (1 SD above the mean for subjects with normal FPG) was the optimum value to detect undiagnosed T2D in this particular sample. Larger cross-sectional and prospective longitudinal studies are needed to confirm these results.

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