Derivation and validation of an HbA1c optimal cutoff for diagnosing prediabetes in a South African mixed ancestry population

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Abstract

Introduction: Prediabetes compromises impaired fasting glucose and impaired glucose tolerance and is a high risk for future diabetes mellitus and cardiovascular disease. Traditional diagnostic methods involve a fasting sample or oral glucose tolerance test, which is cumbersome, time-consuming and inconvenient. An HbA1c-based approach has been incorporated into new guidelines, but cut-offs may vary and have not been defined for all population groups. We derived and validated HbA1c cut-offs to diagnose prediabetes in mixed ancestry South Africans.

Methods: Participants were 667 (derivation sample), 234 (validation sample 1) and 674 (validation sample 2) diabetes-free individuals. They underwent standard 2-hour OGTT with HbA1c test. Receiver-operator characteristic curves were used to determine optimal HbA1c cut-off to predict prediabetes.

Results: A total of 27.7% participants in the derivation sample had prediabetes versus 17.5% (validation sample 1) and 15.4% (validation sample 2). The optimal cut-off was 5.75% in all three cohorts with sensitivity and specificity of 64.8% and 60.4% in combined derivation and validation sample 1, and 59.6% and 69.8% in validation sample 2.

Conclusion: The discriminatory capacity of HbA1c for predicting prediabetes in this population is modest at the derived cut-off. The use of HbA1c alone in this setting may result in an inaccurate diagnosis.

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1. Introduction

Globally, type 2 diabetes mellitus is rising at an alarming rate and has become a health crisis that now threatens economies of all nations. In developing countries, a 69% increase is expected in the next two decades amongst adults compared to a 20% increase in developed countries [1]. Most people with diabetes go through a prediabetic phase for several years during which there is an opportunity to identify them and institute preventative measures [2,3]. The concept of an intermediate state between normoglycaemia and diabetes was first introduced in 1979 by the National Diabetes Data Group. The Expert Committee on the Diagnosis and Classification of Diabetes extended this in 1997 by including subjects with impaired fasting glucose (IFG) in addition to subjects with impaired glucose tolerance (IGT) [4]. Both categories, referred to as prediabetes, are risk factors for the progression to the full stage of type 2 diabetes. The underlying pathology is different in individuals with IFG or IGT with the former having hepatic insulin resistance and the latter being characterized by muscular insulin resistance [5] demonstrating that the two metabolic states have different pathophysiological mechanisms [6]. Although individuals with prediabetes may regress to normoglycaemia or progress to overt diabetes, this stage is also characterized by an increased risk of diabetic microvascular complications and cardiovascular disease [3].

HbA1c is good marker of chronic hyperglycaemia that characterizes diabetes mellitus and has been traditionally used to monitor glycaemic control. However, in 2010, the American Diabetes Association (ADA) incorporated it into clinical practice guidelines to be used for the diagnosis of (≥6.5%) and prediabetes (5.7%–6.4%) [7]. However there is considerable debate about these cut off points. Age, ethnicity, genetic make-up, life span of erythrocytes and degree of glycosylation can all affect these cut-off points. Racial differences, particularly in black populations, in the relationship between blood glucose and HbA1c have been observed [8–11].
According to the revised ADA guidelines of 2010 [7], prediabetes is classified as:

- Impaired glucose tolerance (IGT): 2-hour glucose 7.8–11.1 mmol/l post-75 g oral glucose tolerance test (OGTT) OR
- Impaired fasting glucose (IFG): fasting blood glucose ≥5.6–7 mmol/l OR
- HbA1c level 5.7%–6.4%

The mixed ancestry population of South Africa has one of the highest prevalence rates of diabetes mellitus in Africa and high progression rates from the pre-diabetic stage to diabetes [14]. HbA1c as a screening test that requires no special patient preparation and has good reproducibility might be an ideal test to screen for prediabetes in this population group as both IGT and IFG are traditionally diagnosed during OGTT which is cumbersome, time consuming and impractical. However, the cut-offs for defining pre-diabetes have not been defined for all population groups and may not necessarily agree with the recommended values suggested by ADA. In this study we examined the distribution of HbA1c and explored the optimal cut-off points for identifying subjects with prediabetes in mixed ancestry South Africans.

2. Methods and materials

2.1. Study setting and population

The study setting has been described in details elsewhere [12–14]. Briefly, participants were members of a cohort study conducted in Bellville-South, Cape Town, a mixed ancestry township formed in the late 1950s. Eligible participants were invited to take part in a community based survey between January 2008 and March 2009 (derivation sample), in 2011 the participants were followed up (validation sample 1) and in 2014 another sampling was performed (validation sample 2) with data collection through standardized procedures. The derivation and the validation studies were approved by the Cape Peninsula University of Technology Faculty of Health and Wellness Sciences ethics committee (Reference Number: CPUT/HW-REC 2008/002, CPUT/HW-REC 2010, NHREC: REC-230 408-014 and N14/01/003) as well as the Health Research Ethics Council of the University of Stellenbosch (N09/03/090). The study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants signed written informed consent after all the procedures had been fully explained in the language of their choice.

2.2. Study population

Participants were 667 (derivation sample), 234 (validation sample 1) and 674 (validation sample 2) diabetes free individuals examined respectively in 2008, 2011, and 2014 in the Bellville South Community in Cape Town. Similar procedures were applied for both studies. All consenting participants received a standardized interview and physical examination during which blood pressure was measured according to WHO guidelines [15] using a semi-automated digital blood pressure monitor (Rossmax PA, USA). Other clinical measurements included the body weight, waist and hip circumferences. Participants underwent a standard 2 hour 75 g oral glucose tolerance test, with fasting and 2-hour plasma glucose being determined. IGT and IFG were diagnosed based on revised ADA criteria [7].

2.3. Laboratory measurements

Fasting blood samples were collected and processed for further analysis. Plasma glucose was measured by enzymatic hexokinase method (Cobas 6000, Roche Diagnostics). Glycosylated haemoglobin (HbA1c) was assessed by turbidimetric inhibition immunoassay (Cobas 6000, Roche Diagnostics). This method is National Glycohaemoglobin Standardization Programme (NGSP) certified according to Roche Diagnostics. The follow-up examination in 2011 (3 years from baseline) and the new cohort in 2014 were conducted using similar procedures.

2.4. Statistical methods

General characteristics of the study groups are summarized as count and percentage for qualitative variable, mean and standard deviation (SD) or median and 25th–75th percentiles for quantitative variables. Group comparisons used chi square tests and equivalents for qualitative variables, and Student’s t-test and non-parametric equivalents for quantitative variables, with adjustments where relevant through logistic and linear regression models. The pROC package [16] of the R statistical software version 2.13.0 [13-04-2011] (The R Foundation for Statistical Computing, Vienna, Austria), was used for receiver operating characteristic (ROC) analyses. The area under the curve (AUC) was then used to assess the ability of HbA1c to predict the presence prediabetes [17]. The optimal HbA1c was determined by applying both the Youden’s index approach [18] and the closest top left point approach [19]. Main analyses including the determination of optimal cut-offs were conducted in a sample of participants recruited during the initial survey (derivation sample). The derived cut-offs were then tested in a sample of participants from the same population, recruited during the second evaluation (validation sample 1) and third evaluation (validation sample 2).

3. Results

3.1. Characteristics of the study populations

Table 1 shows the general characteristics of both the derivation and first validation samples (second validation sample in Supplemental material). The derivation sample consisted of 667 participants of which 512 (77%) were women, and the first validation cohort consisted of 234 participants of which 163 (70%) were women. There were some men versus women differences in each cohort, but little evidence of gender × cohort interaction. A total of 185 (27.7%) participants in the derivation cohort, 41 (17.5%) of the validation sample 1 and 104 (15.4%) of the validation sample 2 had prediabetes.

3.2. Optimal HbA1c cut-offs for the diagnosis of prediabetes

Fig. 1 shows the ROC curves for the prediction of prediabetes in the derivation and first validation sample as well as their combination. The area under the ROC curve (AUC) for the prediction of prediabetes was 0.631 in the derivation sample, 0.729 for the validation sample 1 and 0.642 for the combined sample. In the validation sample 2, the AUC was 0.712 in women, 0.501 in men and 0.665 in the overall sample (see Fig. 1 Supplemental data). Table 2 shows the performance of HbA1c thresholds in the different cohorts. The optimal HbA1c cut-off for the diagnosis of prediabetes was 5.75% in the derivation sample (sensitivity 61.1%, specificity 64%); 5.85% in the validation sample 1 (sensitivity 72.5%, specificity 63.3%) and 5.75 in the combination of both (sensitivity 64.8%, specificity 60.4%). Results were mostly similar in men and women. In the validation sample 2, an HbA1c cut-off of 5.75% also emerged as the optimal cut point (Fig. 1 Supplemental data).

4. Discussion

There has been considerable interest in the use of HbA1c to identify individuals who are in the prediabetic state ever since it was recommended for the diagnosis of diabetes in 2010 [7]. This, to the best of our knowledge, is the first study from Africa to report on the optimal HbA1c values that may be used to identify subjects with prediabetes. We found that our optimal cut-off of 5.75% had a sensitivity of 64.8%
and specificity of 60.4% and observed that this value was within the range recommended by the ADA for the diagnosis of prediabetes but lower than the 6% recommended by the International Expert Committee. Furthermore, this cut-off was confirmed in a separate cohort of subjects. However, similar to observations reported in several studies, the discriminatory capacity of HbA1c for predicting prediabetes in our population was modest, with just above average sensitivity and specificity.

Other studies have confirmed this suboptimal performance of HbA1c to identify subjects with prediabetes. Bersoux et al studied 242 patients mean age 62 years in United States of America and found that reliance on HbA1c alone would miss a substantial amount of patients [20]. A study of 5395 individuals from the NHANES study found that an HbA1c value of 5.7% to diagnose prediabetes had a low sensitivity [22]. A study of 5395 individuals from the NHANES study found that the use of HbA1c alone has low sensitivity (AUC .678) [22]. A more recent study by Xu et al. on 98,658 Chinese adults found that an HbA1c value greater than 5.6% had a sensitivity of 68%, a specificity of 94.5% [23].

An Italian study looking at White nondiabetics found that HbA1c led to more subjects being diagnosed with prediabetes than fasting plasma glucose [27]. A study in Bangladesh found that the use of HbA1c alone has low sensitivity (AUC .578) [22]. A study on a cohort of 1370 Palestinian Arabs with no known diabetes aged older than 30 years old compared fasting plasma glucose and HbA1c to diagnose prediabetes. They found the area under the curve for HbA1c to diagnose prediabetes to be 63.9%; the optimal cut-off of HbA1c to diagnose prediabetes was 5.7% and using HbA1c it was 21.5% [24].

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Derivation sample</th>
<th>Validation sample</th>
<th>P</th>
<th>cohort</th>
<th>P gender-cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>667</td>
<td>217</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.7 (15.2)</td>
<td>54.6 (16.7)</td>
<td>50.8 (14.6)</td>
<td>0.015</td>
<td>48.3 (13.8)</td>
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<tr>
<td>FBC (mmol/L)</td>
<td>5.2 (0.7)</td>
<td>5.1 (0.8)</td>
<td>5.3 (0.7)</td>
<td>0.012</td>
<td>5.1 (0.6)</td>
</tr>
<tr>
<td>Post-BG (mmol/L)</td>
<td>6.6 (9.1)</td>
<td>6.4 (1.6)</td>
<td>6.7 (1.6)</td>
<td>0.030</td>
<td>5.7 (1.7)</td>
</tr>
<tr>
<td>Fasting serum insulin (μU/mL)</td>
<td>6.2 (2.7–11.5)</td>
<td>3.9 (1.7–8.0)</td>
<td>7.0 (3.1–12.6)</td>
<td>&lt;0.0001</td>
<td>10.1 (5.9–16.1)</td>
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<tr>
<td>Glucose insulin ratio</td>
<td>0.83 (0.46–1.81)</td>
<td>1.29 (0.64–2.81)</td>
<td>0.73 (0.41–1.60)</td>
<td>&lt;0.0001</td>
<td>0.48 (0.33–0.79)</td>
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<td>HbA1c (%)</td>
<td>5.7 (0.4)</td>
<td>5.7 (0.4)</td>
<td>5.7 (0.4)</td>
<td>0.683</td>
<td>5.8 (0.4)</td>
</tr>
<tr>
<td>Trigs (mmol/L)</td>
<td>1.4 (0.9)</td>
<td>1.4 (0.9)</td>
<td>1.3 (0.9)</td>
<td>0.445</td>
<td>1.4 (0.8)</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>3.6 (1.0)</td>
<td>3.4 (1.0)</td>
<td>3.7 (1.0)</td>
<td>0.003</td>
<td>3.4 (1.0)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.3 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.3 (0.3)</td>
<td>0.007</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.6 (1.2)</td>
<td>5.3 (1.1)</td>
<td>5.4 (1.2)</td>
<td>0.002</td>
<td>5.4 (1.1)</td>
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<td>SBP (mm Hg)</td>
<td>121 (18)</td>
<td>125 (17)</td>
<td>120 (18)</td>
<td>0.0004</td>
<td>130 (23)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>74 (12)</td>
<td>75 (11)</td>
<td>74 (12)</td>
<td>0.113</td>
<td>80 (15)</td>
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<td>Height (m)</td>
<td>1.59 (0.09)</td>
<td>1.68 (0.07)</td>
<td>1.56 (0.07)</td>
<td>&lt;0.0001</td>
<td>1.61 (0.09)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73 (17)</td>
<td>70 (16)</td>
<td>74 (18)</td>
<td>0.016</td>
<td>78 (18)</td>
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<tr>
<td>BMI</td>
<td>29.1 (7.2)</td>
<td>24.9 (5.5)</td>
<td>30.4 (7.1)</td>
<td>&lt;0.0001</td>
<td>30.1 (7.0)</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>109 (14)</td>
<td>99 (9)</td>
<td>112 (14)</td>
<td>&lt;0.0001</td>
<td>108 (13)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>95 (15)</td>
<td>91 (14)</td>
<td>96 (15)</td>
<td>&lt;0.0001</td>
<td>94 (17)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.87 (0.08)</td>
<td>0.91 (0.08)</td>
<td>0.86 (0.07)</td>
<td>&lt;0.0001</td>
<td>0.88 (0.13)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>185</td>
<td>40</td>
<td>145</td>
<td>0.540</td>
<td>41</td>
</tr>
</tbody>
</table>

Fig. 1. Receive operating characteristic curves (ROC) for the prediction of the presence of prediabetes using HbA1c for the derivation and first validation samples. Definition of prediabetes is based on the IDF-WHO criteria-based presence of impaired fasting glycaemia and impaired glucose tolerance following an oral glucose tolerance test and venous blood glucose tests. Area under the ROC curve: 0.631 in the derivation sample, 0.729 in validation sample and 0.642 in total sample. HbA1c optimal cut point: 5.75% [based on both the Youden index and closest-top-left methods: sensitivity (Se) 61.1%, specificity (Sp) 64.0%] in the derivation sample, 5.85% in the validation sample (sensitivity 72.53%, specificity 63.3%), and 5.75 in the total sample (sensitivity 64.8%, specificity 60.4%).
these values that we obtained may not be totally accurate. We performed a single HbA1c test and iron deficiency anaemia, which may increase HbA1c results. Iron deficiency anaemia is common in our population. HbA1c may be unreliable to diagnose prediabetes and diabetes in anaemic patients. Son et al found that anaemic subjects had a higher HbA1c level and suggested that the diagnostic significance of HbA1c may be limited in them [31]. This higher HbA1c was more pronounced in subjects with higher glucose levels. Iron deficiency anaemia reduces erythropoiesis and increases HbA1c levels [32].

A study by Hardikar et al comparing the use of OGTT and HbA1c to diagnose prediabetes found that in iron deficiency anaemia the prevalence of prediabetes was spuriously exaggerated (23.3% (HbA1c) vs 7.8% (OGTT)) [33]. As the Western Cape Province where this study was performed has a relatively high prevalence of iron deficiency anaemia, these values that we obtained may not be totally accurate [34]. We also did not test for haemoglobinopathies, but we do not have high prevalence of haemoglobinopathies in our population. However, its strength was that it was a large study with the cut-off values obtained validated in two separate cohorts.

5. Conclusion

Because there is now strong evidence that lifestyle management in those with prediabetes may reduce the rate of progression to diabetes, it is important to detect those at risk so that prevention efforts can be initiated. These may include lowering the HbA1c levels considerably to detect those at risk in our population. However, recent publications have questioned whether prediabetes may not in fact be an overdiagnosed condition. Yudkin and Montori questioned whether prediabetes is being overdiagnosed since the introduction of HbA1c into the diagnostic criteria [35]. Xu et al. showed a recent prevalence of prediabetes of 50.1% using all three diagnostic criteria which is a dramatic increase compared to previous studies in China before the use of HbA1c [26]. A meta-analysis has shown that more than half the subjects with prediabetes met the diagnostic criteria for diabetes [36]. As only 5 years have passed since the introduction of HbA1c into these diagnostic criteria, we do not have sufficient follow-up studies yet. This potential for overdiagnosis could potentially place further burden on a healthcare budget already overloaded by the HIV and tuberculosis pandemics in the Western Cape.

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### Conflict of interest

None.
Authorship

All authors have made substantial contributions to the following: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting of the article and revising it critically for intellectual content, and (3) final approval of submitted version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cca.2015.06.019.

References


