HbA1c cut points to define various glucose intolerance groups in Asian Indians

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Running title: HbA1c cut points and glucose intolerance in Asian Indians

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**Aim:** To determine glycosylated hemoglobin (HbA1c) cut-points for glucose intolerance in Asian Indians.

**Methods:** 2188 participants without known diabetes were randomly selected from the Chennai Urban Rural Epidemiology Study. All had fasting plasma glucose [FPG] and 2hr post glucose [2hr PG] measurements after 75g load and were classified as impaired fasting glucose [IFG] (ADA criteria: FPG ≥ 5.5 mmol/L and < 7 mmol/L and WHO criteria: FPG ≥ 6.1mmol/L and <7 mmol/L; impaired glucose tolerance [IGT]: 2hr PG ≥ 7.8 mmol/L and < 11.1 mmol/L, or diabetes: FPG ≥ 7mmol/L and / or 2hr PG ≥ 11.1 mmol/L. HbA1c was measured using the Biorad Variant machine. Based on Receiver Operating Characteristic curves, optimum sensitivity and specificity were derived for defining HbA1c cut points for diabetes, IGT and IFG.

**Results:** Mean values of HbA1c among NGT, IGT and diabetes subjects were 5.5±0.4%, 5.9±0.6% and 8.3±2.0% respectively [p for trend <0.001] with considerable overlap. To identify diabetes based on 2hr PG, HbA1c cut point of 6.1% had area under the curve (AUC) of 0.941 with 88.0% sensitivity and 87.9% specificity. When diabetes was defined as FPG ≥ 7.0mmol/L, the HbA1c cut point was 6.4% (AUC=0.966, sensitivity 93.3%, specificity 92.3%). For IGT, AUC = 0.708; IFG – WHO, AUC = 0.632 and IFG – ADA, AUC=0.708, the HbA1c cut point was 5.6%.

**Conclusion:** In Asian Indians, HbA1c cut point of 6.1% and 6.4% defined diabetes by 2hr PG or FPG criteria respectively. A value of 5.6% optimally identified IGT or IFG, but was less than 70% accurate.
Glycated haemoglobin (HbA1c) is an indicator of the average blood glucose concentrations over the preceding 2–3 months and is currently considered the best index of metabolic control in people with diabetes [1]. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that lowering HbA1c can reduce the risk of diabetic microvascular complications [2,3]. Association between HbA1c and cardiovascular risk factors in subjects with normal glucose tolerance [NGT] is also reported [4].

Until recently, HbA1c had not been recommended as a diagnostic or a screening tool because of several factors; lack of standardization, low sensitivity and high cost [5]. However, following efforts at improving standardization of the HbA1c assay and the introduction of the new International Federation of Clinical Chemists (IFCC) standards, HbA1c is now being considered for diagnostic and screening purposes [6]. HbA1c does not need a fasting state or a glucose load, and therefore, offers potential ease and convenience. A recent American Diabetes Association (ADA) international expert committee proposed a HbA1c cut point of 6.5% as a diagnostic test for diabetes [7]. It is important to investigate whether these cut points for HbA1c apply to all populations worldwide. The normative distribution for HbA1c levels has been described in western populations in subjects with normal glucose tolerance [NGT] as well as impaired glucose tolerance [IGT] [8]. However, there are no reports of the normative HbA1c distributions, to our knowledge, from India which currently has the largest number of people with diabetes in the world.

Here, we examine the distribution of HbA1c in a south Indian population, and explore optimal cut-points for identifying diabetes and high-risk prediabetic groups.

RESEARCH DESIGN AND METHODS:

The Chennai Urban Rural Epidemiology Study (CURES) is a cross-sectional population-based study representative of Chennai (formerly Madras), the largest city in southern India with a population of approximately 5 million people. The details of CURES have been previously reported [9]. Briefly, CURES was based on the model of systematic stratified random sampling, wherein, for Phase 1 of the study, 46 of the 155 wards in Chennai were selected for sampling, providing a total sample size of 26,001 individuals ≥ 20 years of age.

In a subsequent phase, every tenth subject recruited in Phase I (n=2,600) were invited for detailed testing, including an oral glucose tolerance test (OGGT) in those without self-reported diabetes, and the response rate was 90% [2350/2600 subjects] [Figure 1]. Anthropometric measurements including weight, height and waist measurements were obtained using standardized techniques [9]. Body mass index (BMI) was calculated using the formula, weight (kg) / height (m²). Blood pressure was recorded in the sitting position in the right arm to the nearest 2mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and the mean of the two was used.
Fasting plasma and 2hr post-load [75gms] plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method) serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method) and HDL cholesterol (direct method-polyethylene glycol-pretreated enzymes) were measured using Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany). The intra and inter assay coefficient of variation for the biochemical assays ranged from 3.1% to 7.6%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.

Of the 2350 subjects who received an OGTT, HbA1c was measured in 2188 subjects (Response rate: 93.1%). Glycated haemoglobin was measured using the Variant machine (Biorad, California). Our centre participates in the Unity programme of Biorad HbA1c standardization. The co-efficient of variation [CV] for HbA1c assay was 3.5%. CV for in-house quality control was <2.5%. In the external quality assessment scheme [EQAS], bias for HbA1c analysis was 1.75% and imprecision, 2.75%, indicating good reproducibility.

Definitions and diagnostic criteria—Diabetes: Diabetes was diagnosed based on the World Health Organization (WHO) consulting Group Criteria [10] i.e, fasting plasma glucose ≥126mg/dl (7 mmol/L) and / or 2hour plasma glucose after an oral glucose tolerance test ≥200 mg/dl (11.1 mmol/L).

Impaired glucose tolerance [IGT]: 2 hr post plasma glucose ≥ 140 mg/dl (7.8 mmol/L) and < 200 mg/dl (11.1 mmol/L) by WHO criteria [10].

Impaired fasting glucose [IFG]: Defined using ADA criteria [11] if fasting plasma glucose ≥100 mg/dl (5.5 mmol/L) and <126 mg/dl (7 mmol/L) and using WHO criteria [10] if fasting plasma glucose ≥110 mg/dl (6.1mmol/L) and <126mg/dl (7 mmol/L).

Normal glucose tolerance [NGT]: Fasting plasma glucose < 100 mg/dl (5.5 mmol/L) and 2 hr post plasma glucose <140 mg/dl (7.8 mmol/L) by WHO criteria [10].

Statistical analysis: Student’s t test or one-way ANOVA [with Tukey’s HSD] were used to compare groups for continuous variables and Chi-square test or Fisher’s Exact test were used to compare proportions. Receiver operating characteristic curves (ROC) were plotted using sensitivity and 1-specificity for different cut points of HbA1c, taking the diagnosis of diabetes, IGT or IFG based on various plasma glucose criteria as the gold standard. Sensitivity was defined by the proportion of subjects with a given risk factor who where identified correctly by a HbA1c value greater or equal to the cut point. Specificity was defined by the proportion of subjects without the risk factor who were identified by a HbA1c value below the cut point. The area under the curve (AUC) was constructed and by interpolation from the area under the curve, the point closest to the upper-left corner, which maximized sensitivity and specificity, was selected as the optimal cut point; this identified the highest number of subjects with or without diabetes, IGT or IFG [12]. Positive and negative predictive values and accuracy for predicting diabetes, IGT and IFG were calculated for different cut points of HbA1c.

RESULTS
Among the 2188 subjects who had both OGTT and HbA1c tests, 1710 (78.2%) had NGT, 258 (11.8%) had IGT, and 220 (10.1%) had newly diagnosed diabetes [NDD]. Subjects with glucose
intolerance [i.e. IGT, NDD] were older compared to subjects with NGT [p<0.01]. Waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, 2hr post plasma glucose, HbA1c, serum cholesterol, serum triglyceride and LDL cholesterol were also higher among subjects with glucose intolerance [IGT and NDD] than in those with NGT. Mean values of HbA1c among NGT, IGT and NDD subjects was 5.5±0.4%, 5.9±0.6% and 8.3±2.0% respectively [p for trend <0.001] (Table 1).

As shown in Table 2, for diabetes, using the 2hr PG ≥ 200mg/dl (11.1mmol/L) criterion, HbA1c cut point of 6.1% had the highest sensitivity and specificity. Using the FPG ≥ 126mg/dl (7.0mmol/L) criterion for diabetes, the optimal HbA1c cut point was 6.4% and for the 2hr ≥ 200mg/dl and FPG ≥ 126mg/dl criterion, the optimal HbA1c cut point was 6.5%. The accuracy of correctly differentiating a person with newly diagnosed diabetes selected at random from the population varied from 90.2% to 95.9% (Table 2), depending on the definition of diabetes and the respective cut-point. For IGT, the optimal HbA1c cut point was 5.6%. For IFG, defined by either the WHO criterion of FPG ≥ 110 (6.1mmol/L) and ≤ 126 mg/dl (7.0mmol/L) or the ADA criterion of FPG ≥ 100 mg/dl (5.6mmol/L) and ≤ 126 mg/dl (7.0mmol), the optimal HbA1c cut point was 5.6%. The accuracy of identifying these prediabetic states ranged around 70%.

Figure 2 shows the distribution of HbA1C in those with NGT, IGT and diabetes. It can be seen that there is considerable overlap between the three categories with respect to the HbA1C levels. The percentage of subjects with NGT, IGT and/or IFG and diabetes identified using various HbA1c cutpoints is shown in Table 3. Using a cut-point of 5.6%, 73.6% of those with IGT and/or IFG (using WHO criteria) and 72.8% of subjects with IFG (using ADA criteria) would get correctly identified. Using the cutpoint of 6.5%, 78.2% of subjects with diabetes would get correctly identified; however 19.4% of IGT and /or IFG (using ADA criteria), 18.1% of IGT and/or IFG (using WHO criteria), and 3.0% of NGT would be included in this category.

DISCUSSION

Our population-based data suggests that HbA1c cut-points of 6.1% and 6.4% are optimal for identifying newly diagnosed diabetes in Asian Indians by 2 hr PG and FPG criteria, respectively. These cut-points can identify diabetes with over 90% accuracy in this population. Additionally, our data suggests that a HbA1c cut-point of 5.6% would identify IGT and/or IFG, subjects with optimal specificity and sensitivity, but the accuracy is only 69-74%.

A large meta-analysis using data from 10 different studies concluded that a HbA1c cut point of 7.0 %, could identify diabetes requiring pharmacological therapy [13]. A population-based study of 3,190 adults of Malay ethnicity concluded that HbA1c levels in the range 6.6 to 7% were optimal for detecting microvascular complications [14]. Studies have also demonstrated that a HbA1c threshold of 6.0% discriminates well between OGTT-diagnosed diabetic and non-diabetic subjects [15, 16].

A recent report by an International Expert Committee has proposed that a diagnosis of diabetes can be made if the HbA1c level is ≥6.5% but the diagnosis should be confirmed with a repeat HbA1c test unless clinical symptoms or glucose levels >200 mg/dl (>11.1 mmol/l) are present [7]. However this was decided based on cross-sectional data on the
relationship between HbA1c and risk of future complications (retinopathy) from western populations. Our data from an Asian Indian population, based on the normative distribution of HbA1c and on its receiver operator characteristics compared to the gold standard test (OGTT), indicates that the HbA1c cut-point appropriate for diagnosing diabetes may be different for non-western populations. Our data suggests an optimal HbA1c cut-point of 5.6% in Asian Indians to identify IGT or IFG, considered prediabetes states and, therefore, target groups for diabetes prevention. The differences in HbA1c cut points in different populations could be due to potential racial and ethnic differences [17-19]. Other factors such as aging, hemoglobin glycation [17, 18, 20] and/or erythrocyte survival [17, 18, 21, 22] could affect the HbA1c assay in addition to heritable factors [23].

The advantages of the HbA1c test are that it can be measured at any time of the day with a small sample of blood and also does not require the cumbersome glucose load. The disadvantages are the difficulty in standardization, cost and that it cannot be measured in the presence of hemoglobin variants [6].

The International Expert Committee suggests a cut point of 6.0% only as an indication for high risk prediabetes states, but not as a strict cut off point. As there is now very strong evidence that lifestyle management of those with IGT can reduce the rate of progression to diabetes [24], it is important to correctly identify those with prediabetes so that prevention efforts may be implemented, without missing those who would benefit from intervention. Our data suggests despite optimal specificity and sensitivity the HbA1c cut-point of 5.6% only has 69-74% accuracy of identifying IGT or IFG. The cutpoint would have to be as low as 5% to identify 97% of all IGT and/or IFG.

One of the strengths of the study is that it is population based and from an Asian Indian population, an ethnic group that has a high susceptibility to type 2 diabetes. Another advantage is the high response rates - 90% of the subjects participated in Phase 3 of CURES, of whom in 93.1% of subjects HbA1c could be done. Thus it is unlikely that there is any significant selection bias. One limitation of our study is that, as it is cross-sectional, one, we cannot assess the ability of HbA1c to predict future diabetes or its micro- and macro-vascular complications. Our focus, however, was to evaluate HbA1c as a screening and diagnostic tool to identify newly diagnosed diabetes or IGT or IFG. Though diabetic subjects in the present study were newly-diagnosed, many had high glycemic and HbA1c values as shown in Figure 2. Had the diagnosis been made earlier, the cut points would perhaps not be so clear cut or accurate.

In summary, our population-based data indicate that for Asian Indians a HbA1c value of ≥ 6.0 may be optimal for diagnosing diabetes with a very high level of accuracy. On the other hand, even a cut-point as low as 5.6%, may miss a substantial proportion of people at high-risk of diabetes who would benefit from proven prevention interventions. While there are merits for a simple and convenient test such as HbA1c to screen for, and diagnose, diabetes and/or high-risk states (such as IGT and/or IFG), it is important that proposals for cut-points to define diabetes and high-risk states duly take into account population differences in HbA1c levels and for this, more studies are clearly needed in non-western populations. Thus there is a need for
more studies including the cost effectiveness of HbA1c vs plasma glucose testing, before HbA1c can be universally recommended as a diagnostic test for diabetes in developing countries. The recommendation for HbA1c to diagnose high risk states is even less clear. Moreover, recognition of individuals with high risk of diabetes can be made on other criteria than glucose regulation only, for example overweight, increased waist circumference, other elements of the metabolic syndrome, etc., which can help to identify people who would need lifestyle modification advice. Indeed, an Indian Diabetes Risk Score was shown to be very effective to screen not only for undiagnosed diabetes, but also for metabolic syndrome and coronary artery disease and is one of the strongest predictors of incident diabetes in an Asian Indian population [25].

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## Table 1: Clinical and biochemical characteristics of study subjects

| Variables                      | NGT [n=1710] | Prediabetes (IFG and IGT) [n=258] | NDD [n=220] |
|--------------------------------|--------------|-----------------------------------|-------------|
| Age (years)                    | 37 ± 12      | 43 ± 13**                         | 45 ± 11**   |
| Body mass index (kg/m²)        | 22.6 ± 4.0   | 24.2 ± 3.5**                      | 24.2 ± 3.1**|
| Waist circumference (cm)       | 81.6 ± 11.4  | 86.9 ± 10.3**                     | 88.5 ± 9.0**|
| Systolic blood pressure (mm Hg)| 115±16.3     | 126.4 ± 19.9**                    | 128.2 ± 21.2**##|
| Diastolic blood pressure (mm Hg)| 72.7 ± 10.8  | 77.4 ± 11.4**                     | 78.8 ± 11.6**|
| Fasting plasma glucose (mmol/L)| 4.6 ± 0.4    | 5.2 ± 0.8**                       | 8.6 ± 3.3**##|
| 2hr post plasma glucose (mmol/L)| 5.5 ± 1.1    | 8.8 ± 1.0**                       | 15.5 ± 3.7**##|
| HbA1c (%)                      | 5.5 ± 0.4    | 5.9 ± 0.6**                       | 8.3 ± 2.0**##|
| Serum cholesterol (mmol/L)     | 4.5 ± 0.9    | 4.8 ± 1.0**                       | 5.0 ± 0.9**|
| Serum triglycerides (mmol/L)   | 1.2 ± 0.7    | 1.6 ± 1.0**                       | 2.1 ± 1.4**##|
| HDL cholesterol (mmol/L)       | 1.1 ± 0.2    | 1.0 ± 0.2*                        | 1.0 ± 0.2**|
| LDL cholesterol (mmol/L)       | 2.8 ± 0.8    | 3.0 ± 0.9**                       | 3.0 ± 0.8**|

**p<0.001 compared to NGT,
#p<0.01, ## p<0.001 compared to IGT
Data presented as mean and SD
LDL cholesterol – Low density lipoprotein
HDL cholesterol – High density lipoprotein
### Table 2: HbA1c cut points with respect to Diabetes, IGT and IFG

| CONDITION | CRITERIA | Mean HbA1c | Optimal HbA1c Cut point | Sens  | Spec  | PPV  | NPV  | AUC  | Accuracy |
|-----------|----------|------------|-------------------------|-------|-------|------|------|------|----------|
| Diabetes  | FPG ≥126mg/dl (10) | 9.2 ± 1.9 | 6.4 | 93.3 | 92.3 | 44.2 | 99.5 | 0.966 | 95.5     |
| Diabetes  | 2Hr ≥ 200mg/dl and FPG ≥126mg/dl (10) | 9.2 ± 1.6 | 6.5 | 92.6 | 93.7 | 46.3 | 99.5 | 0.978 | 95.9     |
| Diabetes  | 2HrPG ≥ 200mg/dl or FPG ≥126mg/dl (10) | 8.3 ± 2.0 | 6.1 | 88.0 | 87.9 | 45.5 | 98.5 | 0.941 | 90.2     |
| Diabetes  | 2Hr ≥ 200mg/dl (10) | 8.3 ± 2.0 | 6.1 | 88.6 | 87.8 | 44.8 | 98.6 | 0.944 | 90.5     |
| IGT       | 2Hr ≥ 140 mg/dl and <200 mg/dl (10) | 5.9 ± 0.6 | 5.6 | 65.6 | 62.1 | 19.9 | 92.6 | 0.708 | 74.1     |
| IFG (WHO) | FBS ≥ 110 mg/dl and <126 mg/dl (10) | 5.7 ± 0.3 | 5.6 | 60.0 | 56.5 | 0.8  | 99.6 | 0.632 | 69.9     |
| IFG (ADA) | FBS ≥ 100 mg/dl and <126 mg/dl (11) | 5.8 ± 0.5 | 5.6 | 65.1 | 63.4 | 8.3  | 97.3 | 0.708 | 70.0     |

**Abbreviations:**
- **AUC:** Area under curve
- **ROC:** Receiver Operating Characteristic curve
- **Sens:** Sensitivity
- **Spec:** Specificity
- **PPV:** Positive predictive value
- **IFG:** Impaired fasting glucose
- **IGT:** Impaired glucose tolerance
- **WHO:** World Health Organization
- **ADA:** American Diabetes Association
Table 3: Proportion of subjects with NGT, IGT and/or IFG and Type 2 diabetes identified using different HbA1c cut points

| HbA1c cut points | NGT | Subjects with IGT and/or IFG [Using ADA criteria] | Subjects with IGT and/or IFG [Using WHO criteria] | NDD |
|------------------|-----|-----------------------------------------------|-----------------------------------------------|-----|
| ≥4.5             | 99.0 % [1621] | 99.6 % [257] | 99.4 % [329] | 99.6 % [224] |
| ≥5.0             | 91.0% [1490]  | 96.5% [249]  | 96.7% [320]  | 99.1% [223]  |
| ≥5.5             | 54.3% [890]   | 79.5% [205]   | 79.8% [264]   | 97.8% [220]  |
| ≥5.6             | 44.7 % [733]  | 73.6% [190]   | 72.8% [241]   | 96.9% [218]  |
| ≥5.7             | 36.6% [599]   | 64.7% [167]   | 65.3% [216]   | 94.7% [213]  |
| ≥5.8             | 28.3% [463]   | 59.7% [154]   | 60.4% [200]   | 94.7% [213]  |
| ≥5.9             | 21.4% [350]   | 52.7% [136]   | 53.5% [177]   | 92.4% [208]  |
| ≥6.0             | 14.9% [244]   | 46.9% [121]   | 47.1% [156]   | 90.2% [203]  |
| ≥6.1             | 10.4% [171]   | 42.6% [110]   | 42.9% [142]   | 89.8% [202]  |
| ≥6.2             | 7.6% [124]    | 34.9% [90]    | 35.0% [116]   | 88.0% [198]  |
| ≥6.3             | 5.6% [91]     | 27.5% [71]    | 27.2% [90]    | 84.9% [191]  |
| ≥6.4             | 3.8% [62]     | 22.1% [57]    | 20.5% [68]    | 81.8% [184]  |
| ≥6.5             | 3.0% [49]     | 19.4% [50]    | 18.1% [60]    | 78.2% [176]  |

IGT – Impaired glucose tolerance, IFG – Impaired fasting glucose, ADA – American Diabetes Association, WHO – World Health Organization, NGT- Normal Glucose Tolerance, NDD- Newly diagnosed diabetes

LEGENDS TO FIGURES

**Figure 1**: Chennai Urban Rural Epidemiology Study (CURES) - Methodology

**Figure 2**: HbA1c distribution among subjects with NGT, IGT and newly diagnosed diabetes [NDD] subjects
HbA1c cut points and glucose intolerance in Asian Indians

Figure 1

Chennai city population (corporation limits) (4,343,645)

Chennai corporation: 10 zones & 155 wards

46 wards were selected

26,001 individuals [age ≥ 20 years] screened

Phase 1
Prevalence of diabetes by ADA criteria

Phase 2
Prevalence of diabetes related complications

Phase 3
Prevalence of metabolic syndrome
Every tenth subject from Phase I (n = 2600)
Response Rate n= 2350 (90%)

For current study, subjects were randomly recruited from Phase III

HbA1C measured in 2188 subjects [93.1%]

NGT
n = 1710

IGT
n = 258

NDD
n = 220
Figure 2

HbA1c cut points and glucose intolerance in Asian Indians

- Normal glucose tolerance
- Impaired glucose tolerance
- Diabetes