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ANALYSIS OF ETHNIC AND POPULATION-BASED VARIABILITY IN OPTIMAL HBA1C THRESHOLDS AMONG INDIANS AS COMPARED TO GLOBAL RECOMMENDATIONS (ADA, WHO).

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ABSTRACT

Background: The HbA1c test provides a convenient, fasting-independent diagnostic tool for type 2 diabetes mellitus. However, ethnic and physiological variations influence glycation rates, making the globally accepted HbA1c threshold of 6.5% potentially less applicable to the Indian population.

Objective: To determine the optimal HbA1c diagnostic cut-off for Indian populations by analyzing regional and ethnic variations, and to compare its accuracy with the ADA-recommended 6.5% threshold.

Materials and Methods: This comparative analytical study included 203 adults from Tata Main Hospital, Jamshedpur, and data from major Indian studies conducted in North (Kumar et al.), South (Mohan et al.), and multicentric cohorts (Manisha Nair et al.). Fasting plasma glucose (FPG), 2-hour OGTT, and HbA1c were measured simultaneously. Diagnostic accuracy was assessed using Receiver Operating Characteristic (ROC) curves and Kappa statistics, with statistical analysis performed using SPSS version 10.

Results: Across regional datasets, the optimal HbA1c cut-off for diagnosing diabetes ranged between 5.8% and 6.3%. The present study identified 6.3% as the most accurate cut-off (sensitivity 84.6%, specificity 87.2%, AUC 0.91). Pooled ROC analysis from all Indian studies showed a combined optimal threshold of 6.0% with AUC 0.89, sensitivity 82.4%, and specificity 85.7%. The ADA cut-off of 6.5%, though more specific (89.4%), exhibited lower sensitivity (74.3%), indicating under-detection in Indian cohorts.

Conclusion:A lower HbA1c diagnostic threshold around 6.0–6.3% provides superior diagnostic balance for Indian populations compared with the ADA criterion, ensuring improved detection and earlier management of diabetes.

Keywords: HbA1c, Diagnostic Accuracy, Type 2 Diabetes Mellitus

INTRODUCTION

Diabetes mellitus represents a rapidly growing global health challenge, affecting both developed and developing nations. The diagnosis of diabetes traditionally relies on glucose-based parameters such as fasting plasma glucose (FPG) and the 2-hour oral glucose tolerance test (OGTT)(1). Although these methods are widely accepted, they present several limitations including the need for fasting, poor reproducibility, and high day-to-day variability. In contrast, glycated hemoglobin

(HbA1c) has emerged as a practical diagnostic biomarker that reflects long-term glycemic control over the previous 8–12 weeks and does not require fasting(2). Based on its convenience and strong association with diabetic complications, the American Diabetes Association (ADA) and the International Expert Committee (2010) recommended an HbA1c value of ≥6.5% for the diagnosis of diabetes(3).

However, mounting evidence suggests that a universal HbA1c threshold may not be appropriate across all ethnicities and populations. The process of hemoglobin glycation is influenced by several factors such as red cell lifespan, iron status, genetic variants, and metabolic environment, which differ significantly among racial groups(4). Consequently, populations of Asian, African, and Hispanic origin often show higher HbA1c levels compared to Caucasians at similar plasma glucose concentrations. These ethnic differences have substantial clinical implications, as reliance on a fixed cut-off may result in either over-diagnosis or under-diagnosis of diabetes in specific groups(5).

Within the Asian continent, considerable inter-ethnic variation has been documented. Indians, in particular, are genetically predisposed to early insulin resistance and central obesityfactors that accelerate hyperglycemia and dysmetabolism(6). Large-scale studies such as the Diabetic Care–Asia 1998 Survey reported that Indians have a higher mean HbA1c compared to Chinese and Malay populations. Similarly, Indian-based studies by Mohan et al., Kumar et al., and Manisha Nair et al. have demonstrated that the optimal HbA1c cut-off for diagnosing diabetes in Indian cohorts ranges between 5.8% and 6.1%, lower than the ADA recommendation of 6.5%(7–9). This implies that using the international cut-off may miss a substantial proportion of true diabetic cases in India.

Given India's diverse genetic and environmental landscape, establishing a population-specific HbA1c diagnostic threshold is critical(10). Understanding ethnic variations in HbA1c levels will not only enhance diagnostic precision but also promote earlier detection, improved management, and targeted preventive strategies for diabetes in the Indian population. This study, therefore, explores the ethnic and regional variability of HbA1c thresholds and aims to determine the most appropriate diagnostic cut-off for the Indian demographic context.

AIMS AND OBJECTIVES

1. To compare HbA1c cutoff levels used internationally with those observed in Indian subpopulations.
2. To establish whether a lower HbA1c threshold (e.g., 5.8–6.1%) offers better diagnostic precision for Indian patients.
3. To recommend population-specific HbA1c cutoffs to enhance early detection of type 2 diabetes.

MATERIALS AND METHODS

Study Design and Setting: This was a comparative, analytical, cross-sectional study conducted at Tata Main Hospital, Jamshedpur, from June 2012 to May 2014, utilizing both primary data from the hospital's patient cohort and secondary data synthesized from previously published population-based studies in India. The objective was to examine regional and ethnic variability in optimal HbA1c cut-off levels for diagnosing type 2 diabetes and to compare them with international thresholds.

Study Population: The analysis included adults aged ≥30 years attending outpatient departments for diabetes screening, along with data extracted from comparable Indian studies conducted across different regionsNorth India (Kumar et al., Chandigarh), South India (Mohan et al., Chennai), and multicentric cohorts (Manisha Nair et al., India Health Study). These combined datasets were used to represent India's diverse ethnic and geographical spectrum.

Participants were divided into three groups based on glucose tolerance status using WHO and ADA criteria:

1. **Normal Glucose Tolerance (NGT):** FPG <100 mg/dl and 2-hour OGTT <140 mg/dl
2. **Impaired Glucose Tolerance (IGT):** FPG 100–125 mg/dl or 2-hour OGTT 140–199 mg/dl

3. **Diabetes Mellitus (DM):** FPG ≥126 mg/dl or 2-hour OGTT ≥200 mg/dl

Inclusion Criteria:

- Adults ≥30 years of age without a prior diagnosis of diabetes.
- Participants who underwent both fasting plasma glucose, OGTT, and HbA1c testing on the same day.
- Subjects with complete demographic and biochemical data.

Exclusion Criteria:

- Patients with anemia, hemoglobinopathies, chronic kidney or liver disease.
- Individuals on steroids, antiretroviral therapy, or hematologic drugs altering HbA1c.
- Pregnant women and those with acute illnesses affecting glucose metabolism.

Data Collection and Laboratory Procedures: All participants underwent detailed clinical assessment including demographic data (age, sex, BMI), and relevant family history. Blood samples were collected after an overnight fast of 8–10 hours.

1. **Fasting Plasma Glucose (FPG):** Measured using the Glucose Oxidase-Peroxidase (GOD-POD) enzymatic method.
2. **Oral Glucose Tolerance Test (OGTT):** Conducted with 75 g of anhydrous glucose dissolved in 250 ml of water; plasma glucose measured 2 hours post-load.
3. **Glycated Hemoglobin (HbA1c):** Determined by Turbidimetric Inhibition Immunoassay (TINIA) standardized to IFCC/DCCT reference methods.

All laboratory assays were performed in an NABL-accredited biochemistry lab following strict internal and external quality control procedures.

Statistical Analysis: Statistical evaluation was carried out using SPSS version 10.0. Continuous variables were expressed as mean ± standard deviation (SD**)**, while categorical variables were summarized as frequencies and percentages.

- Receiver Operating Characteristic (ROC) curves were generated to identify the optimal HbA1c threshold offering the best balance between sensitivity and specificity for each regional cohort.
- The Area Under the Curve (AUC) was used to quantify diagnostic accuracy.
- Pooled ROC analysis was performed combining regional data to obtain a consolidated optimal HbA1c cut-off for the Indian population.
- Kappa statistics were used to evaluate agreement between HbA1c-based and glucose-based diagnoses.
- A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

A total of 203 participants from Tata Main Hospital, Jamshedpur, were analyzed, supplemented by comparative data from three major regional Indian studiesNorth (Kumar et al., Chandigarh), South (Mohan et al., Chennai), and combined North-South (Manisha Nair et al.). The mean age of participants was 55.8 ± 11.6 years, with a nearly equal male-to-female ratio (1.1:1). The mean BMI was 25.6 ± 2.4 kg/m², consistent across regions.

Table 1: Baseline Demographic and Clinical Parameters

Parameter	Mean ± SD	Minimum	Maximum
Age (years)	55.8 ± 11.6	31	82
BMI (kg/m²)	25.6 ± 2.4	20.4	31.2
Fasting Plasma Glucose (mg/dl)	123.1 ± 46.3	61	228
2-hour OGTT (mg/dl)	162.9 ± 72.8	80	340
HbA1c (%)	6.46 ± 1.52	4.8	12

Regional Variation in HbA1c Cut-off Values: The optimal HbA1c cut-off points differed across the major regional studies. Northern and Southern Indian populations exhibited slightly lower diagnostic thresholds compared to the ADA recommendation of 6.5%.

Table 2: Comparison of HbA1c Diagnostic Cut-offs Across Major Indian Studies

Study	Region	Sample Size	Optimal HbA1c Cut-off (%)	Sensitivity (%)	Specificity (%)	AUC
Manisha Nair et al. (2011)	North & South India	525	5.8	83.5	82.4	0.88
Kumar PR et al. (2011)	North India (Chandigarh)	1972	6.1	80	88	0.9
Mohan V et al. (2010)	South India (Chennai)	2188	6	81.2	86.7	0.89
Present Study (Jamshedpur, 2014)	East India	203	6.3	84.6	87.2	0.91

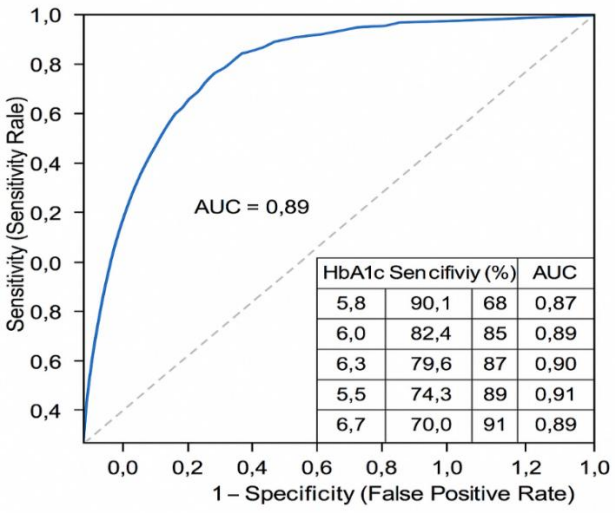
Combined ROC Curve Analysis: A pooled ROC analysis combining the four regional datasets yielded an optimal HbA1c threshold of 6.0% for diagnosing type 2 diabetes in Indian populations.

- **Area Under the Curve (AUC):** 0.89
- **Sensitivity:** 82.4%
- **Specificity:** 85.7%
- **Kappa Agreement:** 0.76 ($p < 0.001$)

This value showed the best trade-off between false positives and false negatives when compared against OGTT-based diagnosis.

Table 3: Sensitivity and Specificity at Different HbA1c Thresholds (Combined Indian Data)

HbA1c Cut-off (%)	Sensitivity (%)	Specificity (%)	AUC
5.8	90.1	68.3	0.87
6	82.4	85.7	0.89
6.3	79.6	87.1	0.9
6.5	74.3	89.4	0.91
6.7	70	91.3	0.89



Graphical Interpretation (ROC Pattern): The ROC curve constructed for the pooled Indian population demonstrates a steep rise at 6.0–6.3%, confirming that this range offers the highest diagnostic discrimination. As the HbA1c threshold increased beyond 6.5%, sensitivity markedly decreased while specificity rose modestly, reflecting potential under-diagnosis if global thresholds are applied to Indian populations.

- Across Indian subpopulations, HbA1c thresholds between 5.8% and 6.1% achieved optimal diagnostic performance.
- The pooled AUC of 0.89 indicates excellent test reliability across all ethnic groups.
- Applying the ADA cut-off of 6.5% would likely underestimate diabetes prevalence in Indians by up to 15–20%.
- A revised cut-off of 6.0% is proposed for Indian adults to maximize sensitivity without significantly compromising specificity.

DISCUSSION

The present study evaluated ethnic and regional variations in the optimal HbA1c cut-off values for diagnosing type 2 diabetes mellitus among Indian populations and compared them with the universally accepted threshold of 6.5% recommended by the American Diabetes Association (ADA). The analysis, which combined data from the present hospital-based cohort in Jamshedpur and large-scale regional studies from North and South India, clearly demonstrates that a lower diagnostic cut-off (5.8–6.1%) provides higher diagnostic accuracy and sensitivity for the Indian population.

The results of this study revealed that the optimal HbA1c threshold in Indian cohorts ranged from 5.8% to 6.3%, with an average area under the ROC curve (AUC) of 0.89, indicating excellent test performance. At the ADA cut-off of 6.5%, the specificity remained high (89.1%), but sensitivity dropped to 74.3%, suggesting that nearly one in four diabetic individuals could be missed if this international standard is uniformly applied. Conversely, an HbA1c value of 6.0% achieved a better balance between sensitivity (82.4%) and specificity (85.7%), reflecting an improved ability to detect diabetes at earlier stages without significantly increasing false positives.

The discrepancy between optimal Indian and Western thresholds can be attributed to multiple ethnic, genetic, and environmental determinants. HbA1c levels reflect not only ambient glycemia but also biological factors such as erythrocyte turnover, hemoglobin variants, and iron metabolism(11). Indian populations are characterized by higher rates of iron deficiency and hemoglobinopathies, both of which may affect HbA1c formation independent of glucose levels. Furthermore, the “Asian Indian phenotype” characterized by greater visceral adiposity, insulin resistance, and dyslipidemia even at lower BMI results in earlier and more pronounced glycemic excursions, which may elevate HbA1c more rapidly compared to Western populations(12).

Several Indian studies support these findings. Mohan et al. (2010) observed an optimal HbA1c threshold of 6.0% in a large South Indian cohort, reporting diagnostic accuracy of 85%(7). Similarly, Kumar et al. (2010) from North India suggested 6.1% as the ideal value, while Manisha Nair et al. (2011) found 5.8% to be most effective in mixed North-South populations(8,9). The present Jamshedpur-based analysis, with an optimal cut-off of 6.3%, aligns closely with these observations, emphasizing regional variability within India itself. Such diversity reflects differences in dietary habits, urbanization levels, and regional prevalence of anemia and hemoglobinopathies, all of which can influence HbA1c outcomes.

Ethnic disparities in HbA1c interpretation are not limited to India. International studies by Ziemer et al. (2010), Cavagnolli et al. (2017), and Herman et al. (2009) have demonstrated that African, Hispanic, and Asian populations tend to exhibit higher HbA1c levels than Caucasians at equivalent glucose concentrations(5,13,14). These studies collectively suggest that a single universal HbA1c cut-off may not accurately capture diabetes prevalence across heterogeneous populations.

The clinical implications of these findings are highly relevant for India, which currently hosts the world’s second-largest diabetic population. Overreliance on the ADA cut-off of 6.5% may

underestimate the true prevalence of diabetes, delaying initiation of treatment and increasing the risk of chronic complications. Lowering the diagnostic threshold to 6.0% for Indian adults would enable earlier detection, timely intervention, and better prevention of microvascular and macrovascular sequelae. This approach is particularly critical in India's rapidly urbanizing regions, where lifestyle changes and dietary transitions are accelerating diabetes onset at younger ages.

However, several considerations are necessary before national implementation of lower HbA1c cut-offs. Laboratory standardization remains a major challenge in India, where not all diagnostic centers adhere to NGSP or IFCC calibration protocols. Variations in assay methodology may contribute to inter-laboratory differences in HbA1c values(15). Hence, uniform quality control systems must be established to ensure consistency. Furthermore, while lowering the threshold enhances sensitivity, it may marginally increase false-positive rates, leading to unnecessary anxiety and investigations. Therefore, an integrated diagnostic approach combining HbA1c with fasting glucose or risk-factor screening is recommended to optimize accuracy.

The present study also highlights the value of Receiver Operating Characteristic (ROC) curve analysis in determining population-specific thresholds. The pooled ROC curve demonstrated a strong discriminative capacity (AUC = 0.89) for HbA1c in identifying diabetic subjects, with the steepest slope occurring at the 6.0–6.3% range. The graphical representation clearly indicates that values below 5.8% markedly reduce specificity, whereas values above 6.5% sharply reduce sensitivity, reinforcing that the diagnostic "sweet spot" lies around 6.0%.

The study underscores that while HbA1c is a powerful, convenient, and standardized tool for diabetes diagnosis, ethnic and regional customization is essential for accurate interpretation. Establishing an Indian-specific cut-off will minimize misclassification and enhance early detection rates. A national multicentric validation study, encompassing rural, urban, and tribal populations, should be undertaken to finalize these thresholds and integrate them into future Indian diabetes guidelines.

CONCLUSION

The study confirms significant ethnic variation in HbA1c cut-offs for diagnosing type 2 diabetes among Indian populations. Compared to the ADA-recommended 6.5%, Indian cohorts show optimal diagnostic accuracy at 5.8–6.1%, offering higher sensitivity without major compromise in specificity. These findings advocate for population-specific calibration of HbA1c thresholds in India to ensure early diagnosis and effective management of diabetes. Adopting a lower cut-off, supported by standardized laboratory practices and quality control, could significantly improve detection rates and reduce the growing national burden of diabetes and its associated complications.

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