

# The limitations and fallacies of relying on glycosylated hemoglobin for diagnosing and monitoring diabetes in Indian populations

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## Summary

Glycated hemoglobin (HbA1c) is commonly used to diagnose and monitor type 2 diabetes (T2D). However, in South Asia—particularly India—the high prevalence of anemia, hemoglobinopathies, and glucose-6-phosphate dehydrogenase (G6PD) deficiency, and poorly standardized HbA1c assay methods complicates the interpretation of HbA1c values, challenging its reliability in both diagnosis and monitoring of diabetes. Overall, reliance solely on HbA1c is constrained by several clinical and biological factors in India. A multiparametric, risk-stratified approach that integrates oral glucose tolerance test, self-monitoring of blood glucose, and whenever possible, continuous glucose monitoring, in addition to relevant hematologic assessments are essential to enhance diagnostic and monitoring accuracy and inform appropriate treatment decisions, especially in primary care and resource-limited settings.

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In the Indian subcontinent, the rising number of people with type 2 diabetes (T2D)<sup>1</sup> makes it essential to maintain good glycemic control to prevent a substantial burden of diabetes-related complications.<sup>2</sup> It is imperative that T2D is properly diagnosed and monitored to reduce this burden and avoid adverse outcomes.<sup>3</sup> Further, accurate diagnosis is required for prediabetes and diabetes for appropriate management.

In this respect, most clinicians rely on glycated hemoglobin (HbA1c) for the diagnosis and management of T2D. Its practical advantages are well known: the test does not require fasting, reflects glycemic trends over the preceding two to three months, and has been broadly adopted in clinical guidelines, including those of the World Health Organization<sup>4</sup> and the American Diabetes Association.<sup>5</sup> However, it is

important to recognize that the clinical roles of HbA1c in diagnosing versus monitoring diabetes are distinct, and each may be affected differently by patient and laboratory factors.

However, its widespread use—and the tendency toward oversimplification by both physicians and patients—can lead to misinterpretation, particularly in populations with altered erythrocyte dynamics, such as those with anemia or hemoglobinopathies.

The assumption that HbA1c uniformly reflects glycemic control across all individuals, regardless of genetic, hematologic, or metabolic variation, is increasingly difficult to justify in some populations, such as Asian Indians.

## Search strategy and selection criteria

We conducted a structured search of PubMed (MEDLINE), Scopus, and Google Scholar to identify relevant English-language publications from January 1990 to October 2025. Search terms included

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combinations of “HbA1c,” “glycated hemoglobin,” “diabetes diagnosis,” “oral glucose tolerance test (OGTT),” “iron deficiency anemia,” “hemoglobinopathies,” “G6PD deficiency,” “polycythemia,” “erythrocyte lifespan,” “South Asians,” and “India.” Filters were applied to select observational studies, randomized controlled trials, meta-analyses, national survey reports, and clinical guidelines. Studies were grouped based on whether they evaluated HbA1c as a diagnostic tool (e.g., compared to the OGTT or fasting blood/plasma glucose [FBG/FPG]) or as a monitoring marker (e.g., compared to self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM), fructosamine, or glycated albumin). This was done to ensure that the distinct clinical roles of HbA1c in diagnosis and monitoring were assessed separately.

Observational studies, randomized trials, meta-analyses, and consensus guidelines were included if they provided data on:

- Discordance between HbA1c and glucose-based indices
- Diagnostic or monitoring performance in the presence of hematologic disorders
- Alternative biomarkers such as fructosamine, glycated albumin, or 1,5-anhydroglucitol.

Special emphasis was given to studies that examined hematological conditions affecting HbA1c values—such as anemia, sickle cell disease,  $\beta$ -thalassaemia, G6PD deficiency, and polycythemia—and their regional burden in South Asia. We sought evidence on whether certain methods are more reliable in the presence of these variants and how clinicians can interpret local, assay-specific limitations. This article aims to critically examine the limitations of HbA1c as a standalone tool for diagnosing and monitoring diabetes in Indian and South Asian populations. It highlights the impact of prevalent hematologic disorders, genetic variants, and assay variability on HbA1c accuracy. The goal is to advocate for a more reliable, multiparametric and risk-stratified approach to glycemic assessment in these settings.

### Discordance of HbA1c with blood glucose levels

Since the link between glucose regulation and hemoglobin glycation was established in 1976, HbA1c has become the gold standard for assessing glycemic control. In 2010, HbA1c was also proposed for the diagnosis of prediabetes and diabetes, owing to its convenience (no requirement for fasting blood draw), pre-analytic stability, and relatively low intra-individual variability.<sup>6</sup>

Despite these advantages, the utility of HbA1c as a diagnostic and monitoring tool has been questioned, as

it may not always reflect actual blood glucose levels.<sup>6</sup> In patients with type 1 diabetes, a non-linear relationship between mean blood glucose and HbA1c has been documented.<sup>7</sup> Notably, glucose levels during the preceding 30 days account for approximately 50% of the HbA1c value, while the remaining 50% reflects glycemia over the prior 90–120 days.<sup>8</sup> Data from the Diabetes Prevention Program showed that fasting plasma glucose alone often underrepresents glycemic burden, whereas postprandial glucose—particularly after lunch—correlates more closely with HbA1c.<sup>9</sup>

Further evidence from continuous glucose monitoring systems (CGMS) reveals significant variability in mean glucose concentrations at any given HbA1c level.<sup>10</sup> For instance, an HbA1c of 8.0% corresponds to a 95% prediction interval for mean glucose ranging from 155 to 218 mg/dL—substantially overlapping with intervals for HbA1c levels of 7.0% (128–190 mg/dL) and 9.0% (182–249 mg/dL).<sup>10</sup> Whether average glucose is estimated via fasting plasma glucose,<sup>11</sup> 7-point self-monitoring of blood glucose,<sup>12</sup> or 12-week continuous monitoring,<sup>13</sup> discordance with HbA1c remains evident. These data suggest that HbA1c may under-, or overestimate mean glucose levels in individual cases.

A key driver of this discordance is biological variation in red blood cell lifespan, intracellular glycation kinetics, and individual metabolic regulation of hemoglobin glycation. To quantify such variation, researchers have proposed two related indices: the Glycation Gap (GGap) and the Hemoglobin Glycation Index (HGI). The GGap is calculated as the difference between HbA1c predicted from plasma fructosamine (a marker of short-term glycemia) and the measured HbA1c. The HGI reflects individual variation in hemoglobin glycation beyond glucose levels; it is defined as the difference between an observed HbA1c and the predicted value derived from fasting plasma glucose using a population-based regression model.<sup>14</sup> Both indices demonstrate intra-individual stability and help explain why individuals with similar glycemic profiles may exhibit clinically divergent HbA1c values.<sup>15,16</sup>

The reliability of HbA1c as a marker varies based on whether it is being used for diagnosis or for monitoring. In diagnostic settings, discordant results may lead to misclassification of diabetes status, especially in individuals with coexisting conditions like anemia or hemoglobinopathies. During monitoring, misleading HbA1c levels may obscure short-term glycemic fluctuations or treatment responses.

### Divergence between HbA1c and blood glucose in India: effect of prevalent hematological abnormalities

These considerations are particularly pertinent to India. Various causes of divergence between HbA1c and blood glucose values are given in [Table 1](#).

Cause	Mechanism(s)	Reference
Hemoglobinopathies (e.g., sickle cell disease, thalassemia)	Abnormal hemoglobin variants and reduced red cell lifespan may alter glycation kinetics, leading to falsely low or high HbA1c levels depending on the variant and assay method.	17
G6PD (glucose-6-phosphate dehydrogenase) enzyme deficiency	Subclinical hemolysis shortens red cell lifespan, reducing glycation and causing falsely low HbA1c levels. This may delay diagnosis and increase the risk of complications.	18
Iron deficiency anemia (IDA)	Increased glycation of young erythrocytes and prolonged red cell lifespan may falsely elevate HbA1c, independent of actual glycemia.	19
Hemolytic anemia	Reduced erythrocyte lifespan limits glycation time, yielding falsely low HbA1c despite hyperglycemia—especially when erythrocyte lifespan drops below ~74 days.	20
Recent blood transfusion	Donor red blood cells (RBCs) may dilute or distort HbA1c depending on their age and glycation. Effects are modest but can be clinically significant.	21
Polycythemia	Elevated RBC count, as seen in high-altitude induced polycythemia or other conditions with erythrocytosis, prolongs erythrocyte lifespan, allowing more time for glycation and leading to falsely elevated HbA1c values.	22
Acute blood loss	Loss of mature RBCs increases the proportion of young, less-glycated cells, transiently lowering HbA1c levels.	23
Chronic renal failure	Accumulation of carbamylated hemoglobin in uremia and altered erythropoiesis with reduced red cell survival can interfere with HbA1c measurement.	24
Pregnancy	Increased red blood cell turnover and plasma volume expansion may lower HbA1c, resulting in underestimation of glycemic exposure. Additionally, iron deficiency anemia and vitamin deficiency-related anemias are common and may further confound HbA1c interpretation.	25
Elderly	A negative association has been observed between age and HbA1c in individuals with diabetes, independent of disease characteristics, complications, and inflammatory markers. This link is stronger in those with lower red cell distribution width, suggesting that red cell morphology may influence HbA1c levels with aging.	26
High-dose vitamin C	It may interfere with certain HbA1c assays or reduce glycation via antioxidant effects, possibly lowering HbA1c values.	27
Alcohol abuse	This condition alters glucose metabolism, liver function, and RBC turnover, leading to unreliable HbA1c levels.	28
Liver disease	Chronic liver disease alters erythropoiesis and shortens RBC lifespan due to hypersplenism, bleeding, and medication effects, leading to falsely low HbA1c levels.	29
High BMI	Obesity may influence RBC lifespan, systemic inflammation, or glycation kinetics, leading to underestimation of glycemia by HbA1c.	30
Race (e.g., non-Hispanic Blacks, South Asians)	Racial and ethnic differences can affect HbA1c levels independent of glycemia, contributing to under- or overestimation.	31-34
Other factors	Conditions such as asplenia, hypertriglyceridemia (>1750 mg/dL), hyperbilirubinemia (>20 mg/dL), lead poisoning, opioid/salicylate use, ribavirin therapy, and vitamin E ingestion may skew HbA1c levels. Assay variation also contributes. Additionally, seasonal variation has been observed, with monsoon-related peaks and autumn lows in Indian population, possibly due to climate, diet, or infection patterns.	35,36
Unexplained variability	This is likely due to unidentified biological, genetic, or enzymatic mechanisms that are not yet fully understood.	37

**Table 1: Common causes of discrepant HbA1c values vs blood glucose and underlying mechanisms.**

Several studies show relationship and mismatch between HbA1c and glucose levels in India. In a recent cross-sectional study of 1120 Asian Indians in south India, OGTT identified far more cases of prediabetes (87.8%) than HbA1c (45.4%), with minimal overlap ( $\kappa = 0.09$ ).<sup>38</sup> In 1972 adults in north India, HbA1c cut-offs recommended by the American Diabetes Association (ADA, 5.7%) and International Expert Committee (IEC, 6.0%) showed moderate accuracy, but significantly underdiagnosed prediabetes compared with oral glucose tolerance test. The two criteria identified different prediabetic cohorts, highlighting the need for long-term validation studies.<sup>32</sup> In a study involving 683 adults from South India's Rayalaseema region, both fasting plasma glucose (FPG) and 2-h post-load glucose (2-hPG) values from OGTT were compared with HbA1c to derive a diagnostic threshold for T2D. An HbA1c cut-off of >6.3% (45 mmol/mol) showed strong diagnostic performance, with a sensitivity of 90.6% and specificity of 85.2% in the training dataset

and was successfully validated in a separate dataset with similarly high accuracy. When applied to a group of 238 participants who only underwent FPG and HbA1c testing, 65.8% of those with FPG  $\geq 126$  mg/dL had HbA1c >6.3%, while 90.2% of those without diabetes had HbA1c  $\leq 6.3\%$ , demonstrating good agreement. The authors state that these findings support the use of HbA1c >6.3% as a population-appropriate threshold for diagnosing T2D in this South Indian cohort.<sup>39</sup> Another study in South India showed that an HbA1c value below 7% was significantly affected by red cell turnover indices; therefore, the authors advised that clinicians confirm diabetes or prediabetes using plasma glucose measurements. While no single hemoglobin or mean corpuscular volume value could predict discordance, a red cell distribution width (RDW) value >17 was consistently associated with discordance across all the HbA1c strata. Based on these data, they stated that in individuals with a RDW greater than 17, HbA1c should be replaced by a 75-g OGTT as the preferred diagnostic

method.<sup>33</sup> Further, in a cohort of 116 young adults from the Pune Children's Study, HbA1c identified a higher prevalence of prediabetes (23.3%) compared to the OGTT (7.8%). HbA1c demonstrated a high negative predictive value (93%) but a low positive predictive value (20%) against OGTT-defined dysglycaemia, which was further reduced among anemic individuals (7%). Anemia and low ferritin levels independently contributed to elevated HbA1c concentrations, apart from glycemia. As the authors caution, relying on HbA1c to diagnose prediabetes or diabetes in iron-deficient populations may lead to overestimation of disease prevalence.<sup>34</sup> These findings underline the need for caution in relying solely on HbA1c in Asian Indian populations, where hematological abnormalities are common, and reinforces the value of OGTT as a confirmatory diagnostic tool in these settings.

Further data from global studies are also available. In a major study, authors used data from 117 population-based studies and quantified, in different world regions, the prevalence of diagnosed diabetes, and whether those who were previously undiagnosed and detected as having diabetes in survey screening, had elevated FPG, HbA1c or both. Among those with screen-detected diabetes with either test, the age-standardized proportion who had elevated levels of both FPG and HbA1c was 29–39% across regions; the remainder had discordant elevation of FPG or HbA1c. The authors state, "In most low- and middle-income regions, isolated elevated HbA1c was more common than isolated elevated FPG. In these regions, the use of FPG alone may delay diabetes diagnosis and underestimate diabetes prevalence".<sup>40</sup>

There are several factors which may affect mismatch of HbA1c and blood glucose levels in India, as discussed in detail in the following sections. In India, several population-level hematologic conditions complicate the interpretation of HbA1c, most notably the widespread burden of iron deficiency anemia (IDA). A comprehensive meta-analysis of 157 cross-sectional studies conducted between 1995 and 2023 reported an overall anemia prevalence of 53% (95% CI: 48%, 59%) among adults aged 19–59 years, with substantial regional variation—ranging from 64% in the Northern region to 39% in the North-East. Among adults aged 60 years and older, prevalence ranged from 52% to 68%, peaking in the Eastern region at 65%.<sup>41</sup> In this analysis, anemia—including presumed IDA—was defined using World Health Organization criteria: hemoglobin levels <13 g/dL in men, <12 g/dL in non-pregnant women, and <11 g/dL in pregnant women. While iron studies were not consistently available across all included reports, microcytic hypochromic anemia was widely considered a surrogate marker for iron deficiency.<sup>41</sup> IDA alters erythrocyte lifespan and turnover, potentially leading to either falsely elevated or suppressed HbA1c values depending on the timing and severity of

the deficiency (Table 1).<sup>42</sup> This distortion is especially relevant in rural and underserved regions, where populations are nutritionally compromised and IDA often goes undiagnosed or untreated.<sup>43</sup>

Other red cell disorders further compound this challenge. The estimated national prevalence of sickle cell disease (SCD), sickle cell trait (SCT), and hemoglobin S-beta-thalassemia is 1.17% (95% CI, 0.79%–1.75%), 5.9% (95% CI, 3.8%–8.88%), and 0.37% (95% CI, 0.17%–0.83%), respectively.<sup>44</sup> Regional states such as Madhya Pradesh, Chhattisgarh, and Maharashtra report higher rates of these disorders, particularly among the tribal populations. India accounted for 21% of global SCD births in 2000, a proportion that declined to 16% by 2021, yet the country continues to bear one of the highest disability burdens worldwide from this condition.<sup>45</sup> These hemoglobinopathies are associated with shortened erythrocyte lifespan and altered hemoglobin structure, both of which compromise HbA1c reliability.

Similar findings have also been reported in some south-east Asian countries. In the study from Thailand, 34.3% of 845 diabetic patients had abnormal hemoglobin types, including 30.2% with heterozygous HbE, 1.9% with homozygous HbE, 1.4% with Hb Constant Spring trait, 0.2% with CSEA Bart's, and 0.6% with beta-thalassemia trait. The authors highlighted the potential inaccuracy of HbA1c measurements in individuals with hemoglobin variants, particularly in those lacking HbA expression. These authors further inferred that in the population with a high prevalence of hemoglobinopathies, hemoglobin typing should be considered as basic information prior to HbA1c measurement<sup>46</sup>

### G6PD deficiency: a recently identified factor in discordance between HbA1C and blood glucose values and delayed diagnosis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is another underrecognized cause of discordance between glycemia and HbA1c. G6PD deficiency, an X-linked enzymatic disorder that impairs redox homeostasis, predisposes erythrocytes to oxidative damage and hemolysis.<sup>47,48</sup> Even in the absence of overt hemolysis, the condition may silently shorten red cell lifespan, thereby lowering HbA1c values independently of glycemia. In a recently published large genomic study involving over 500,000 participants from the UK Biobank and Genes & Health cohorts, Martin *et al.*<sup>18</sup> identified substantial underdiagnosis of G6PD deficiency among South Asian and African males. Among South Asian men, 1 in 63 were carriers of clinically significant variants—most commonly rs5030868 (G6PD c.202G > A; p. Val68Met)—yet fewer than 2% had a formal diagnosis. These carriers exhibited a mean HbA1c reduction of ~0.9 percentage

points (approximately 10 mmol/mol) without a corresponding difference in mean blood glucose. Importantly, this discordance resulted in a median delay of 4.1 years in diabetes diagnosis and a 37% increase in microvascular complications.<sup>18</sup> In this context, it is relevant to note that a meta-analysis found G6PD deficiency in 8.5% of the Indian population, with prevalence being especially high in tribal groups.<sup>49,50</sup>

Taken together, these findings underscore the limitations of a uniform HbA1c-based approach in India. High rates of IDA (affecting an estimated 25%–68% depending on age, sex, and study region), hemoglobinopathies ((0.37%–5.9%), with regional and ethnic variation), and G6PD deficiency (7.7–8.5%)<sup>49,50</sup> suggest that a considerable proportion of Indian adults—especially those with or at risk for diabetes—may have distorted HbA1c readings (Table 1).

Additionally, variability in the standardization of HbA1c assays in India remains a concern. Many laboratories use methods other than High-performance liquid chromatography (HPLC) for the assessment of HbA1c. Even ion-exchange HPLC, which is widely employed in Indian laboratories, may yield aberrant or uninterpretable results in individuals with silent hemoglobin variants. In a large cohort study of over 42,000 patients in Spain, Lorenzo-Medina *et al.*<sup>51</sup> found 160 abnormal HPLC chromatograms; 134 showed significant discordance between HbA1c and fasting plasma glucose. A survey of 147 National Accreditation Board for Testing and Calibration Laboratories-accredited laboratories in India found that while glucose testing was universal, HbA1c testing was available in 87% of labs but poorly standardized. Significant variation existed in test nomenclature, methodology, and analytical performance.<sup>52</sup> A survey of 310 Indian laboratories found that 75% used HbA1c for diabetes mellitus diagnosis, but only 70% of these assays were National Glycohaemoglobin Standardization Programme (NGSP)-certified. Participation in proficiency testing for HbA1c was limited, highlighting gaps in quality assurance. The study emphasized the need for wider adoption of standardized, NGSP-certified HbA1c methods to improve diabetes diagnosis and management in India.<sup>53</sup>

Interestingly, seasonal variations in HbA1c levels have been seen in Indians. A study of 8138 Indian patients found seasonal variations in HbA1c levels, with peaks during the monsoon (June–September) and the lowest levels in autumn (October–November). Patients with well-controlled diabetes exhibited higher HbA1c levels during winter and the monsoon, whereas those with HbA1c  $\geq 6.5\%$  showed lower values during the monsoon and autumn.<sup>36</sup>

A summary of key regional studies comparing HbA1c with glucose-based diagnostic criteria is presented in Table 2. These concerns highlight the need

for alternative and complementary approaches to assess Glycemia.

### Beyond HbA1c: alternative and complementary approaches to assess glycemia

When discordance between HbA1c and actual glycemic control is suspected, alternative strategies should be considered. These may be employed alongside HbA1c or in a sequential manner. Self-monitoring of blood glucose (SMBG) remains an indispensable tool for daily glycemic assessment, particularly in resource-limited settings. However, SMBG provides only intermittent data and fails to capture long-term glycemic trends or variability.<sup>58</sup>

Fructosamine which reflects glycemic control over the preceding 2–3 weeks offer accurate short-term indicator when hemoglobin-based metrics are unreliable.<sup>59</sup> Fructosamine has shown good correlation with HbA1c for monitoring glycemic control among Southeast Asians.<sup>60</sup> However, its clinical use is constrained by higher cost and limited availability across laboratories in India.

Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) technologies provide real-time glycemic metrics such as Time in Range (TIR), Time Above Range (TAR), Time Below Range (TBR), and the Glucose Management Indicator (GMI), which correlate well with glycemic control and clinical outcomes.<sup>61,62</sup> Several studies have compared SMBG with CGM and have demonstrated advantages of CGM, particularly in the detection of hypoglycaemia. In a randomized comparison of the two methods in people with T2D, structured and consistent use of glucose data—irrespective of the device used (structured SMBG or CGM)—was associated with improvements in HbA1c control.<sup>63</sup> Despite their clinical utility, CGM systems remain prohibitively expensive, have limited geographic accessibility in India, may provide incomplete data depending on usage patterns, and sensors need to be replaced regularly. Finally, accuracy may also be compromised in certain physiological conditions.

Additionally, glycated albumin (GA) reflects glycemia over a 2–3-week period by measuring nonenzymatic glycation of serum albumin. It serves as a reliable short-term alternative to HbA1c, particularly when red blood cell turnover is altered. Unlike HbA1c, GA is unaffected by conditions such as hemolytic anemia, iron deficiency anemia, or hemoglobinopathies, making it more accurate in these settings. GA has also demonstrated stronger correlations with postprandial glucose excursions and glycemic variability, particularly in patients with type 1 diabetes and those undergoing rapid glycemic shifts, such as during pregnancy or initiation of therapy. However, its interpretation is limited in disorders affecting albumin metabolism—such as nephrotic syndrome, liver dysfunction, and thyroid disease—and it

Study	Population & design	HbA1c cut-offs & comparator	Key findings/relevance	Tests for Hemoglobin, Iron, other hematological indices and variant hemoglobin
Radhakrishna <i>et al.</i> (2018) <sup>54</sup>	332 high-risk South Indian adults	Compared HbA1c with FPG and 2-hPG (on OGTT); HbA1c cut-offs: 6.5% (T2D), 5.9% (prediabetes)	HbA1c $\geq$ 6.5% had high sensitivity (95.8%) and specificity (96.2%). HbA1c had the least short-term variability.	ND
Venkataraman <i>et al.</i> (2012) <sup>55</sup>	3895 adults without known diabetes in Singapore (Chinese, Malays, Indians)	Evaluated HbA1c vs FPG; explored ethnic variation	HbA1c levels were higher per unit of FPG among Indians and Malays compared to Chinese. Ethnicity influenced HbA1c–glucose relationship.	ND
Bhowmik <i>et al.</i> (2013) <sup>56</sup>	2293 rural Bangladeshi adults; no known diabetes; cross-sectional OGTT-based study	HbA1c $\geq$ 6.0% optimal for diabetes; $\geq$ 5.6% for prediabetes	HbA1c 6.0% showed 86.2% sensitivity, 93.3% specificity. Recommended lower cut-offs for South Asians.	Hemoglobin measured; iron and variant hemoglobin not tested.
Basit <i>et al.</i> (2020) <sup>57</sup>	6836 individuals from the 2nd National Diabetes Survey of Pakistan	Compared OGTT with HbA1c; optimal HbA1c cut-offs: 5.7% (T2D), 5.1% (prediabetes)	HbA1c showed poor agreement with OGTT. Suggested region-specific diagnostic criteria due to underdiagnosis at international thresholds.	ND
Kumar <i>et al.</i> (2025) <sup>38</sup>	1120 South Indian adults from the Kerala Diabetes Prevention Program; cross-sectional analysis	Compared HbA1c (5.7–6.4%) with OGTT-based impaired fasting glucose and impaired glucose tolerance.	OGTT identified 87.8% with prediabetes vs 45.4% by HbA1c. Only 65 individuals (5.8%) fulfilled all three criteria (IFG, IGT, and elevated HbA1c).	ND
Bhansali <i>et al.</i> (2012) <sup>32</sup>	1972 adults ( $\geq$ 20 years) from urban Chandigarh, India; cross-sectional community survey using stratified systematic random sampling	Compared ADA cut-off (5.7%) and IEC cut-off (6.0%) with WHO 1999 OGTT criteria	HbA1c 5.7%: Sensitivity 62%, Specificity 77%; HbA1c 6.0%: Sensitivity 36%, Specificity 90%. Both cut-offs underdiagnosed prediabetes (38% and 64% missed, respectively). Recommended OGTT remains more sensitive in this population.	HbA1c tested using HPLC <sup>a</sup> . Iron status not assessed
Mohan <i>et al.</i> (2016) <sup>39</sup>	921 adults from Andhra Pradesh, South India; cross-sectional hospital-based study. OGTT and HbA1c were performed in 683 participants (342 for derivation, 341 for validation).	HbA1c cut-off $>$ 6.3% (45 mmol/mol) derived using ROC against OGTT (FPG $\geq$ 126 mg/dL and/or 2-h-PG $\geq$ 200 mg/dL)	HbA1c $>$ 6.3% demonstrated high diagnostic performance, with a sensitivity of 90.6% and specificity of 85.2%, and was validated with a sensitivity of 88.8% and specificity of 81.9%, making it suitable for use in this South Indian cohort.	HbA1c measured using HPLC <sup>a</sup> .
Kannan <i>et al.</i> 2019 <sup>33</sup>	237 non-diabetic adults from Northeast India; cross-sectional study	Compared concordance/discordance between HbA1c and plasma glucose (FPG and 2-h PPBG).	HbA1c values $<$ 7% showed significant discordance with plasma glucose in 44% of participants. Discordance was most common in the 6.5–7% HbA1c range (72%). RDW $>$ 17 was a consistent marker of discordance across all HbA1c strata.	Hematological indices measured, hemoglobin, MCV, MCH, MCHC, RDW, platelets. Iron status (ferritin, iron studies) and hemoglobin variants were not tested.
Hardikar <i>et al.</i> 2012 <sup>34</sup>	116 young adults from the Pune Children's Study; cross-sectional analysis	HbA1c 5.7–6.4% (prediabetes) and $\geq$ 6.5% (diabetes) per ADA 2009 vs OGTT (WHO 2006)	HbA1c identified 23.3% as prediabetes vs 7.8% by OGTT; positive predictive value was low (20%), especially among anemic individuals (7%). HbA1c was independently influenced by low hemoglobin and low ferritin	Hemoglobin measured; detailed red cell indices (MCV, MCH, MCHC, RDW, platelets) assessed. Iron status (ferritin) evaluated. HbA1c measured by HPLC <sup>a</sup> . No hemoglobinopathies found.

ND, not done; FPG, fasting plasma glucose; 2-hPG, Two-hour post-oral load glucose; OGTT, oral glucose tolerance test; HbA1c, glycated haemoglobin; ADA, American Diabetes Association; IEC, International Expert Committee; WHO, World Health Organization; HPLC, High Performance Liquid Chromatography; ROC, receiver operating characteristic; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width. <sup>a</sup>HbA1c was tested by high-performance liquid chromatography (HPLC) using the Bio-Rad D-10 analyzer, a method that additionally identifies common hemoglobin variants and hemoglobinopathies

**Table 2: Summary of south Asian studies comparing HbA1c with glucose-based tests for diagnosing prediabetes and diabetes.**

remains underutilized in India due to cost and restricted laboratory availability.<sup>64</sup> Improving detection of dysglycaemia by combining HbA1c and GA has shown to be more useful in African population.<sup>65</sup>

Further, 1,5-anhydroglucitol (1,5-AG) is a naturally occurring monosaccharide that serves as a sensitive marker of short-term hyperglycaemia, especially postprandial excursions. Its serum levels decline rapidly in the presence of glucosuria, as urinary glucose competitively inhibits renal reabsorption of 1,5-AG. This inverse relationship allows 1,5-AG to detect glycemic fluctuations over the prior 1–2 weeks—especially in patients with moderate to good glycemic control, where HbA1c may miss transient spikes. Unlike HbA1c, it is unaffected by altered red blood cell kinetics or hemoglobin variants. However, 1,5-AG is unreliable in chronic kidney disease or persistent glucosuria and remains largely unavailable in India due to high cost, limited access, and lack of assay standardization.<sup>66</sup> Its use in clinical practice is, therefore, currently limited, but future feasibility studies may help assess its place in Indian diabetes care.

Use of metrics such as the Hemoglobin Glycation Index (HGI) can further enhance precision. HGI quantifies the discordance between measured HbA1c and mean glucose, capturing individual variations in glycation rates. A low HGI is clinically relevant, as it indicates that HbA1c may underestimate actual hyperglycaemia, thereby masking the risk of complications. In India, however, the clinical application of HGI requires validation using population-specific regression equations, as glycation dynamics may differ across ethnic and regional groups.

A tailored, risk-stratified approach to glycemic monitoring—outlined in Table 3—should become an integral part of national clinical practice. This framework aligns monitoring intensity, biomarker selection, and hematologic screening with the level of healthcare resources and patient-specific factors. Comprehensive diagnostic workups—including complete blood count, reticulocyte count, iron studies, hemoglobin electrophoresis, and G6PD testing—should be incorporated into diabetes care pathways, particularly in tribal, rural, or underserved populations where red cell disorders are highly prevalent.

Assessment domain	Low-resource settings (Primary/secondary care)	Middle-high resource settings (Tertiary care/private)
Primary glycemic monitoring	Self-monitoring of blood glucose (SMBG) <ul style="list-style-type: none"> <li>Frequency: Fasting and 2-hr. post-meals, 2–3 × /week</li> <li>Glucose meter with adequate test strips</li> <li>Focus on paired testing (pre-/post-meal)</li> </ul>	<ul style="list-style-type: none"> <li>SMBG</li> <li>Continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) targets for non-pregnant adults with diabetes:                             <ul style="list-style-type: none"> <li>Time in Range (TIR, 70–180 mg/dL): &gt;70%</li> <li>Time Below Range (TBR, &lt;70 mg/dL): &lt;4%</li> <li>Time Above Range (TAR, &gt;180 mg/dL): &lt;25%</li> </ul> </li> </ul>
Alternative glycemic markers	Not routinely used	<ul style="list-style-type: none"> <li>Fructosamine</li> <li>Glycated albumin (GA)<sup>a</sup></li> <li>1,5-Anhydroglucitol (1,5-AG)<sup>a</sup></li> </ul>
Further workup	Not routinely used	Hemoglobin Glycation Index (HGI) <sup>b</sup>
Hematologic workup	Basic screening: <ul style="list-style-type: none"> <li>Hemoglobin/Hematocrit</li> <li>Peripheral blood smear</li> <li>Red cell distribution width</li> <li>Reticulocyte count (optional)</li> <li>Serum ferritin (optional)</li> </ul>	Comprehensive evaluation: <ul style="list-style-type: none"> <li>Red cell distribution width (RDW)</li> <li>Iron panel (ferritin, serum iron, TIBC, transferrin saturation)</li> <li>Vitamin B<sub>12</sub> and folate</li> <li>Reticulocyte count and index</li> <li>Mean corpuscular volume (MCV)</li> </ul>
Hemoglobinopathies screening	Targeted screening: Clinical suspicion-based, especially in high-risk populations: <ul style="list-style-type: none"> <li>Tribal communities</li> <li>Endemic regions</li> </ul>	Comprehensive screening: <ul style="list-style-type: none"> <li>Hemoglobin electrophoresis</li> <li>Sickle solubility test</li> <li>Genetic testing for β-thalassemia, sickle cell, HbE, HbD variants</li> </ul>
G6PD (glucose-6-phosphate dehydrogenase) deficiency assessment	<ul style="list-style-type: none"> <li>Clinical history-based screening: Prior hemolysis after infection, drug exposure (e.g., sulfonamides, antimalarials), fava bean ingestion, or neonatal jaundice in male infants</li> <li>Semi-quantitative rapid diagnostic tests (if available, optional)</li> </ul>	<ul style="list-style-type: none"> <li>Quantitative G6PD enzyme assay</li> <li>Genetic testing for common variants (e.g., rs5030868, Mediterranean)</li> </ul>
Cost considerations	<ul style="list-style-type: none"> <li>Glucose meter: “₹500–1500” (\$6–18)</li> <li>Glucose testing strips: “₹15–25”/strip (\$0.18–0.30)</li> <li>Self-monitoring of blood glucose: “₹450–750”/month (30 tests) (\$5.40–9.00)</li> <li>Basic complete blood count (CBC): “₹150–400” (\$1.80–4.80)</li> <li>HbA1c: “₹300–600” (\$3.60–7.20)</li> </ul>	<ul style="list-style-type: none"> <li>CGM: “₹3000–8000”/month (\$36–96)</li> <li>Hemoglobin electrophoresis: “₹800–2000” (\$9.60–24.00)</li> <li>G6PD (quantitative): “₹1000–2500” (\$12.00–30.00)</li> <li>Fructosamine: “₹400–800” (\$4.80–9.60)</li> <li>Complete iron panel: “₹1200–2500” (\$14.40–30.00)</li> </ul>

₹, Indian National Rupee; \$, US Dollar; costs given here are approximations. <sup>a</sup>Not routinely available. <sup>b</sup>Requires population specific regression equations. Note: Application of these tests requires an individualised approach and clinical judgement.

Table 3: Beyond HbA1c—risk-stratified approach to glycemic monitoring in India.

### Clinical and policy implications

For diagnosis of prediabetes or T2D, standardized OGTT should remain the gold standard for diagnosis. HbA1c may be used to corroborate this diagnosis but should not serve as the sole diagnostic tool, particularly in populations with prevalent hematological abnormalities. In areas where hemoglobinopathies or anemia are endemic, an OGTT is preferred for accurate classification. For monitoring, HbA1c (measured using a standardized and NGSP-certified assay) should be interpreted alongside serial fasting and postprandial blood glucose values. Both measures should complement each other in long-term glycemic assessment. Where available and affordable, CGMS may provide additional insights into glycemic variability.

### In cases of major discordance between HbA1c, CGM, or SMBG values

Hematologic parameters should be routinely assessed, particularly the RDW. When RDW is elevated or discordance persists, a targeted work-up—including complete blood count, peripheral blood smear, iron studies, and hemoglobin electrophoresis should be considered. A full hematological evaluation may not be necessary at every HbA1c measurement, but it should be done intermittently, especially when new symptoms arise or glycemic markers diverge significantly.

### For national policy and research

Prevalence data from India should not rely solely on HbA1c, as doing so may lead to overestimation of prediabetes and diabetes, particularly in regions with high anemia or hemoglobinopathy burdens. This can result in misleading public health assessments<sup>67,68</sup> and misallocation of resources in national policy. National surveillance programs must ensure assay standardization across laboratories, promote the use of glucose-based testing (e.g., OGTT or fasting and postprandial plasma glucose), and support context-specific interpretation of HbA1c data. Where possible, regional prevalence of hematologic conditions should guide diagnostic algorithm selection. A simple and accurate diagnostic test should be developed for India, building on previous efforts made in this direction<sup>69</sup>. Finally, in urban settings, primary care physicians should ensure HbA1c assays are performed using validated methods and interpreted in conjunction with CBC and clinical history. In rural or tribal populations—where iron deficiency, G6PD deficiency, and hemoglobinopathies are more common—OGTT and SMBG may offer more reliable guidance. Physicians should remain alert to discordant readings and adjust diagnostic or treatment strategies accordingly.

### Conclusion

The use of HbA1c as a standalone diagnostic or monitoring tool is often questionable in South Asian

populations. Persistently high rates of anemia, inherited hemoglobin variants, enzymatic red cell disorders, and poorly standardized HbA1c measurement instruments can produce misleading values—leading to underdiagnosis, inappropriate treatment decisions, and delayed initiation of care. As India and neighboring countries expand their diabetes prevention and management programs, diagnostic algorithms must evolve toward more multiparametric, risk-stratified approaches that integrate clinical, biochemical, and hematologic data.

### Contributors

SSS contributed to the writing of the original draft, literature search, data collection and formal analysis. SRJ contributed to study design, data interpretation, validation and critical review of the manuscript. AM made the major contribution to conceptualization, study design, methodology, interpretation of findings, manuscript review and editing. NKV contributed to the editing and literature search. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

### Data sharing statement

The manuscript has used publicly available data.

### Declaration of interests

We declare no competing interests.

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