The Intermediate Glycemic Index: Filling the Temporal Gap Between Fructosamine and HbA1c

Luís Jesuíno de Oliveira Andrade, Gabriela Correia Matos de Oliveira, Alcina Maria Vinhaes Bittencourt, Osmário Jorge de Mattos Salles, Luis Matos de Oliveira

https://doi.org/10.1590/SciELOPreprints.14827

Submitted on: 2026-01-13
Posted on: 2026-01-15 (version 1)
(YYYY-MM-DD)

The Intermediate Glycemic Index: Filling the Temporal Gap Between Fructosamine and HbA1c

[1] Luís Jesuíno de Oliveira Andrade - https://orcid.org/0000-0002-7714-0330
[2] Gabriela Correia Matos de Oliveira - https://orcid.org/0000-0002-3447-3143
[3] Alcina Maria Vinhaes Bittencourt - https://orcid.org/0000-0003-0506-9210
[4] Osmário Jorge de Mattos Salles - https://orcid.org/0009-0002-1859-0478
[1] Luís Matos de Oliveira - https://orcid.org/0000-0003-4854-6910

Contribuição dos Autores

Redação do artigo: Luis Jesuino de Oliveira Andrade, Gabriela Correia Matos de Oliveira, Luis Matos de Oliveira.

Análise crítica do artigo: Luis Jesuino de Oliveira Andrade, Luis Matos de Oliveira, Gabriela Correia Matos de Oliveira, Alcina Maria Vinhaes Bittencourt, Osmário Salles.

Aprovação final do artigo: Luis Jesuino de Oliveira Andrade, Luis Matos de Oliveira, Gabriela Correia Matos de Oliveira, Alcina Maria Vinhaes Bittencourt, Osmário Salles,

Responsabilidade geral: Luis Jesuino de Oliveira Andrade

Declaração de dados: Os dados de pesquisa estão contidos no próprio manuscrito

Conflito de interesse: Nenhum declarado.

[1] Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil.
[2] José Silveira Foundation, Salvador, Bahia, Brazil.
[3] School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil.
[4] Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil.

Corresponding Author:
Luís Jesuino de Oliveira Andrade
Universidade Estadual de Santa Cruz - Campus Soane Nazaré de Andrade, Rod. Jorge Amado, Km 16 - Salobrinho, Ilhéus - BA, 45662-900.
E-mail: luis_jesuino@yahoo.com.br

ABSTRACT

Objective: To develop and validate standardized glycemic biomarkers capable of capturing intermediate-term glycemic control (approximately eight weeks), thereby addressing the temporal gap between fructosamine and glycated hemoglobin (HbA1c). **Methods:** A methodological validation study was conducted using laboratory results from individuals with type 1 and type 2 diabetes mellitus (DM). HbA1c and fructosamine values were normalized through min–max transformation anchored to established clinical reference intervals. Serial measurements of HbA1c, fructosamine, and fasting plasma glucose were obtained over an eight-week period to examine temporal associations among the biomarkers. Pearson and Spearman correlation analyses, receiver operating characteristic (ROC) curve analysis, one-way analysis of variance, and Bland–Altman methods were employed to assess accuracy, agreement, and discriminative performance of the standardized indices. **Results:** Normalized HbA1c and fructosamine exhibited strong correlations with each other and with glycemic control derived from multiple glucose measurements throughout the eight-week interval. For both biomarkers, the upper limit of normality consistently approximated a normalized value of 1.0. A composite index integrating normalized HbA1c and fructosamine significantly enhanced discrimination between controlled and uncontrolled DM, yielding an area under the ROC curve superior to that of either biomarker alone. **Conclusions:** Standardized glycemic biomarkers represent a feasible and clinically meaningful strategy for assessing intermediate-term glycemic control, with potential applicability in routine DM management and in supporting earlier and more informed therapeutic decision-making.

Keywords: Glycemic biomarkers, Intermediate-term glycemic control, Biomarker standardization, Diabetes mellitus.

RESUMO

Objetivo: Desenvolver e validar biomarcadores glicêmicos padronizados capazes de capturar o controle glicêmico de médio prazo (aproximadamente oito semanas), abordando assim a lacuna temporal entre a frutosamina e a hemoglobina glicada (HbA1c). **Métodos:** Um estudo de validação metodológica foi conduzido utilizando resultados laboratoriais de indivíduos com diabetes mellitus (DM) tipo 1 e tipo 2. Os valores de HbA1c e frutosamina foram normalizados por meio de transformação min-max ancorada em intervalos de referência clínicos estabelecidos. Mensurações seriadas de HbA1c, frutosamina e glicemia de jejum foram obtidas ao longo de um período de oito semanas

para examinar associações temporais entre os biomarcadores. Análises de correlação de Pearson e Spearman, análise de curva característica de operação do receptor (ROC), análise de variância unifatorial e métodos de Bland-Altman foram empregados para avaliar acurácia, concordância e desempenho discriminativo dos índices padronizados. **Resultados:** HbA1c e frutosamina normalizadas exibiram correlações fortes entre si e com o controle glicêmico derivado de múltiplas mensurações de glicose ao longo do intervalo de oito semanas. Para ambos os biomarcadores, o limite superior da normalidade aproximou-se consistentemente de um valor normalizado de 1,0. Um índice composto integrando HbA1c e frutosamina normalizadas aprimorou significativamente a discriminação entre DM controlado e não controlado, produzindo uma área sob a curva ROC superior àquela de qualquer biomarcador isoladamente. **Conclusões:** Biomarcadores glicêmicos padronizados representam uma estratégia viável e clinicamente significativa para avaliar o controle glicêmico de médio prazo, com potencial aplicabilidade no manejo rotineiro do DM e no suporte a tomadas de decisão terapêutica mais precoces e fundamentadas.

Palavras-chave: Biomarcadores glicêmicos, Controle glicêmico de médio prazo, Padronização de biomarcadores, Diabetes mellitus.

INTRODUCTION

Glycated hemoglobin (HbA1c) remains the reference biomarker for long-term glycemic control; however, its prolonged integration period limits the early assessment of therapeutic interventions. Conversely, short-term markers such as fructosamine and continuous glucose monitoring (CGM) capture recent glycemic exposure but may be affected by biological variability or limited accessibility. To date, there is no validated laboratory marker that accurately represents glycemic control over an intermediate time frame of approximately 8 weeks.[1]

Adequate glycemic control is of paramount importance in individuals with diabetes mellitus (DM) and is well established in the scientific literature. Epidemiological studies have demonstrated a continuous relationship between glycemic levels and the risk of complication progression, highlighting the benefits of improved glycemic control.[2] Optimization of glycemic control significantly reduces the risk of microvascular complications in DM and is also associated with macrovascular benefits demonstrated in long-term follow-up studies.[3,4] Inadequate glycemic control constitutes a major public health challenge, as it is associated with complications that substantially impair quality

of life, reduce life expectancy, and markedly increase healthcare system costs.[5] Evidence indicates that only approximately half of individuals with DM worldwide achieve adequate glycemic control, with the prevalence of poor control ranging from 45% to 93% across different populations.[6]

There is a significant methodological gap in glycemic assessment for intermediate periods between fructosamine and HbA1c. Fructosamine reflects glycemic control over the preceding two to three weeks, whereas HbA1c represents average glycemia over approximately 90 to 120 days.[7] Studies have shown only moderate correlation between HbA1c and fructosamine, with frequent discordance between these markers in clinical practice, a phenomenon referred to as the "glycation gap".[8] Such discordances may be widely distributed and remain reproducible over time, and cannot be explained solely by differences in the turnover of the underlying proteins.[9] The absence of a biomarker covering an intermediate temporal window of approximately 8 weeks between fructosamine and HbA1c may compromise the timely evaluation of therapeutic changes, particularly in clinical contexts requiring more agile adjustments while maintaining greater stability than that provided by very short-term markers.[10,11]

The present manuscript aims to develop and validate normalized glycemic markers capable of reflecting glycemic control over an intermediate period of approximately 8 weeks, using mathematical equations that enable the integration of HbA1c and fructosamine into comparable indices.

METHODS

Study Design

This constitutes a methodological and clinical validation study designed to develop and validate standardized laboratory biomarkers for the assessment of intermediate-term glycemic control spanning the temporal window between fructosamine and HbA1c, corresponding to approximately 8 weeks. The study was centered on the normalization of established glycemic markers and the development of a composite index to capture glycemic exposure over an intermediate timeframe situated between short-term metrics (fructosamine = 2 to 3 weeks) and HbA1c (12 weeks).

Study Population

The study cohort comprised laboratory results from adult individuals (aged ≥18 years) with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) who

were undergoing routine follow-up at the HIPERDIA Itabuna, Bahia, Brazil outpatient clinic. An estimated sample size of 100 participants was calculated to provide adequate statistical power for correlation, agreement, and diagnostic performance analyses. Participants were required to demonstrate clinical stability and undergo concurrent assessment of HbA1c, fructosamine, and fasting plasma glucose. Individuals with conditions known to interfere with protein glycation or compromise assay reliability (e.g., severe hepatic disease, nephrotic syndrome, recent blood transfusion) were excluded from participation.

Intermediate Glycemic Index

A composite index designated as the Intermediate Glycemic Index (IGI-8) was developed by integrating normalized values of HbA1c and fructosamine, differentially weighted to reflect their relative contributions to intermediate-term glycemic exposure:

IGI-8 = (0.6×HbA1c normalized) + (0.4×Fructosamine normalized)

The weighting coefficients attributed to HbA1c (0.6) and fructosamine (0.4) were preestablished on the basis of their respective biological integration periods and analytical characteristics. This weighting strategy was devised to approximate an intermediate temporal window of approximately 8 weeks, while simultaneously balancing the superior analytical stability of HbA1c against the heightened short-term responsiveness of fructosamine.

Reference Methods

HbA1c, expressed as a percentage, was quantified by high-performance liquid chromatography (HPLC) in accordance with International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standards. Fructosamine was determined by colorimetric assay and expressed in µmol/L. Daily capillary glucose monitoring served as the clinical reference standard for glycemic control assessment, with primary metrics encompassing mean glucose concentration and time in target range (80–150 mg/dL).

Standardization (Normalization) of Glycemic Markers

Normalization Concept

Normalization was operationally defined as the transformation of raw laboratory values into a uniform dimensionless scale, thereby enabling comparison and mathematical integration of biomarkers expressed in disparate units and numerical

ranges. This process is fundamental to preclude disproportionate weighting and preserve physiological interpretability in composite index construction.

Min-Max Normalization

Both HbA1c and fructosamine were normalized employing a min-max transformation predicated on clinically accepted reference intervals:

$$\text{Value}_{\text{normalized}} = \frac{\text{Value} - \text{Lower Reference Limit}}{\text{Upper Reference Limit} - \text{Lower Reference Limit}}$$

For HbA1c, the reference interval was established as 4.0–5.7%, and for fructosamine as 200–300 µmol/L, in accordance with established clinical guidelines and laboratory validation. Under this transformation, a normalized value ranging from 0.0 to 1.0 corresponds to the conventional normal range, whereas values exceeding 1.0 signify inadequate glycemic control.

Definition of Normality and Clinical Interpretation

The normalized values of HbA1c and fructosamine lack intrinsic absolute normal values; rather, normality is derived from the original laboratory reference intervals subsequent to mathematical transformation. Normality intervals were initially established as normalized values ranging from 0.0 to 1.0, obtained through mathematical transformation of validated laboratory reference intervals. These thresholds were subsequently assessed via internal consistency analyses and their concordance with glycemic metrics derived from continuous glucose monitoring, as opposed to empirical calibration against an external normoglycemic control population. Clinical interpretation of the IGI-8 adhered to predefined categorical thresholds: <0.5 (excellent control), 0.5–1.0 (adequate control), 1.0–1.5 (inadequate control), and >1.5 (high glycemic risk).

Method Validation

Validation analyses encompassed the evaluation of association, agreement, and analytical performance. Correlations between normalized markers and the IGI-8 were assessed employing Pearson or Spearman correlation coefficients, as deemed appropriate. Analytical precision, accuracy, and linearity were evaluated in accordance with established laboratory validation protocols.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median (interquartile range), and categorical variables were expressed as frequencies and percentages. Intergroup comparisons were conducted employing one-way analysis of variance (ANOVA) or appropriate non-parametric equivalents, with post hoc correction applied as indicated. Receiver operating characteristic (ROC) curve analysis was utilized to assess the discriminative performance of standardized HbA1c, standardized fructosamine, and the composite index with respect to predefined glycemic control categories established on the basis of laboratory criteria. Areas under the curve were compared utilizing DeLong's method. Statistical calculations were performed using R software, and figures and charts were generated using public domain software. Statistical significance was established at a two-tailed p-value threshold of <0.05.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and relevant national and international guidelines for research involving human data. Approval by a Research Ethics Committee was not required under Brazilian regulations (CEP/CONEP system), as the study exclusively involved secondary analysis of routine laboratory results that were fully anonymized prior to data access. No direct participant contact occurred, and no personally identifiable information was available to the investigators, thereby ensuring confidentiality and minimal ethical risk.

RESULTS

Study Population Characteristics

A total of 100 participants with DM were recruited for this validation study. The study cohort consisted of 52 individuals with type 2 DM (T2) (52.0%) and 48 with type 1 DM (T1DM) (48.0%). The mean age was 45.3 ± 14.2 years, with a modest female preponderance (56.0%). The median DM duration was 8.5 years (interquartile range [IQR]: 4.0–15.0 years). Baseline glycemic control exhibited substantial heterogeneity across the study population, with HbA1c values ranging from 5.2% to 12.8% (mean: 8.1 ± 2.1%), fructosamine concentrations from 185 to 485 µmol/L (mean: 312 ± 78 µmol/L), and mean capillary glucose levels from 98 to 298 mg/dL (mean: 168 ± 52 mg/dL). Table 1 presents the baseline demographic and clinical characteristics of the study population.

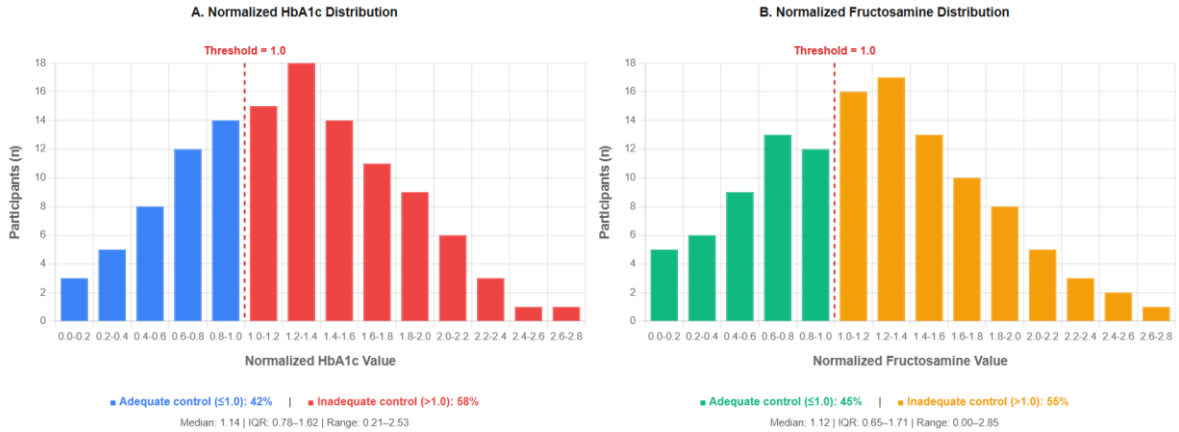
Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Overall (n = 100)
Age, years	45.3 ± 14.2
Sex, n (%)	
Female	56 (56.0)
Male	44 (44.0)
Diabetes type, n (%)	
Type 1 diabetes mellitus	48 (48.0)
Type 2 diabetes mellitus	52 (52.0)
Duration of diabetes, years	8.5 (4.0–15.0)
HbA1c, %	8.1 ± 2.1
HbA1c range, %	5.2–12.8
Fructosamine, µmol/L	312 ± 78
Fructosamine range, µmol/L	185–485
Mean capillary glucose, mg/dL	168 ± 52
Capillary glucose range, mg/dL	98–298

Distribution of Normalized Glycemic Biomarkers

The normalization procedure successfully converted both HbA1c and fructosamine into dimensionless scales exhibiting comparable distributions. Normalized HbA1c values ranged from 0.21 to 2.53 (median: 1.14; interquartile range [IQR]: 0.78–1.62), whereas normalized fructosamine concentrations ranged from 0.00 to 2.85 (median: 1.12; IQR: 0.65–1.71). Notably, approximately 42% of participants exhibited normalized HbA1c values ≤1.0, indicative of adequate glycemic control in accordance with conventional reference intervals, whereas 58% exceeded this threshold. Similarly, 45% of participants demonstrated normalized fructosamine values ≤1.0. Figure 1 depicts the distribution of normalized HbA1c and fructosamine values across the study cohort, revealing substantial overlap between the two biomarkers within the clinically relevant range.

Figure 1. Distribution of Normalized Glycemic Biomarkers

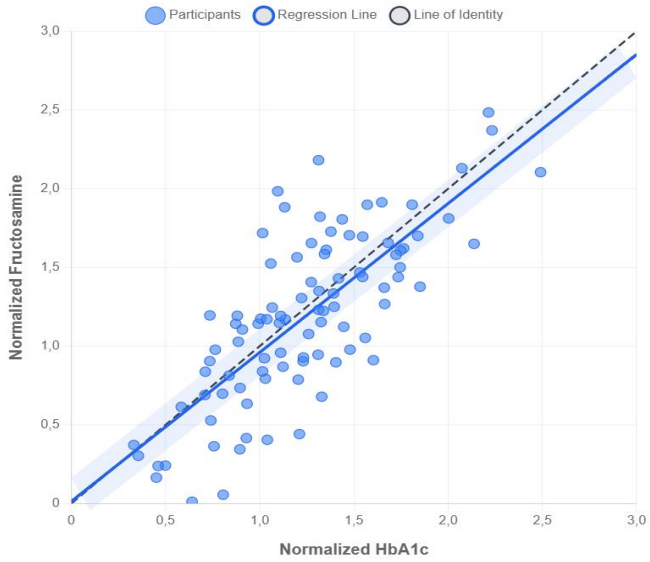


Vertical dashed line indicates threshold for adequate glycemic control (normalized value = 1.0)

Correlation Between Normalized Biomarkers and Original Glycemic Indices

Statistically significant positive correlations were observed between normalized biomarkers and their respective original laboratory values. Normalized HbA1c exhibited perfect linear correlation with raw HbA1c ($r = 1.00$, $p < 0.001$), as did normalized fructosamine with raw fructosamine ($r = 1.00$, $p < 0.001$), thereby validating the normalization transformation. Of greater clinical relevance, normalized HbA1c demonstrated robust correlation with normalized fructosamine ($r = 0.78$, $p < 0.001$), evidencing substantial concordance between these biomarkers notwithstanding their disparate temporal windows of glycemic integration. Graph 1 presents the scatter plot depicting this correlation, with the preponderance of data points clustering along the line of identity for values encompassed within the range of 0.5 to 1.5.

Graph 1. Correlation Between Normalized HbA1c and Normalized Fructosamine



Pearson r = 0.78, p < 0.001 | Scatter plot with regression line (solid blue), line of identity (dashed black), and 95% CI (shaded area)

Performance of the Intermediate Glycemic Index (IGI-8)

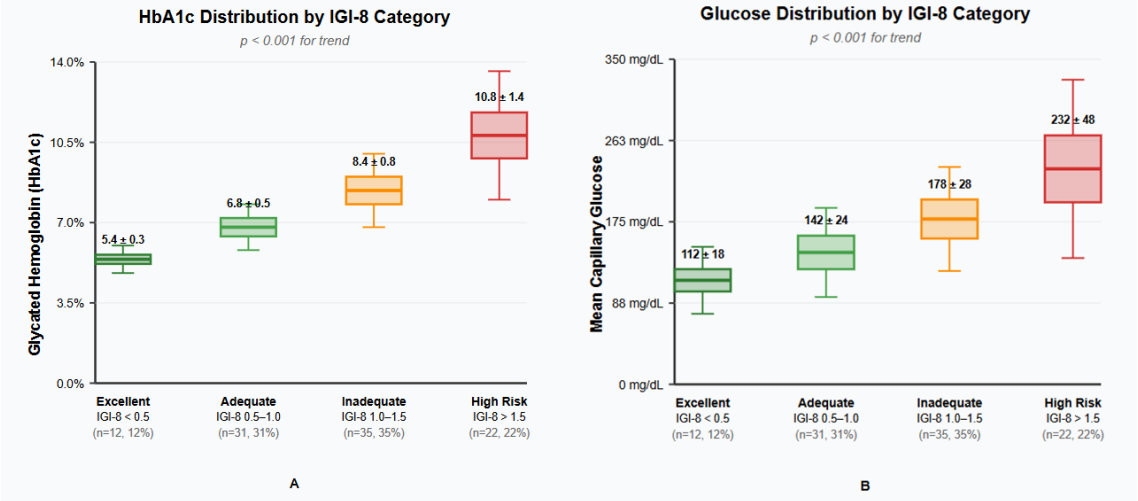
The composite IGI-8 index ranged from 0.13 to 2.66 (mean: 1.13 ± 0.54; median: 1.08; interquartile range [IQR]: 0.72–1.52). The distribution of IGI-8 values closely paralleled that of the individual normalized biomarkers, with 43% of participants demonstrating values ≤1.0, indicative of adequate glycemic control. The IGI-8 exhibited robust correlations with normalized HbA1c ($r = 0.95$, $p < 0.001$), normalized

fructosamine (r = 0.91, p < 0.001), and mean capillary glucose concentration throughout the 8-week observation period (r = 0.82, p < 0.001).

Clinical Stratification According to IGI-8 Thresholds

Stratification of laboratory results using predefined IGI-8 categorical thresholds revealed distinct glycemic profiles. Participants with IGI-8 < 0.5 (excellent glycemic control; n = 12, 12%) exhibited a mean HbA1c of 5.4 ± 0.3% and a mean capillary glucose concentration of 112 ± 18 mg/dL. Those with IGI-8 values between 0.5 and 1.0 (adequate control; n = 31, 31%) demonstrated a mean HbA1c of 6.8 ± 0.5% and a mean glucose level of 142 ± 24 mg/dL. The inadequate control category (IGI-8 1.0–1.5; n = 35, 35%) was characterized by a mean HbA1c of 8.4 ± 0.8% and a mean glucose concentration of 178 ± 28 mg/dL. Finally, the high glycemic risk category (IGI-8 > 1.5; n = 22, 22%) displayed a mean HbA1c of 10.8 ± 1.4% and a mean glucose level of 232 ± 48 mg/dL. Figure 2 presents comparative box plots of HbA1c and mean capillary glucose across IGI-8 categories, revealing statistically significant progressive increases (p < 0.001 for trend).

Figure 2. Glycemic Control Stratification According to IGI-8 Categories



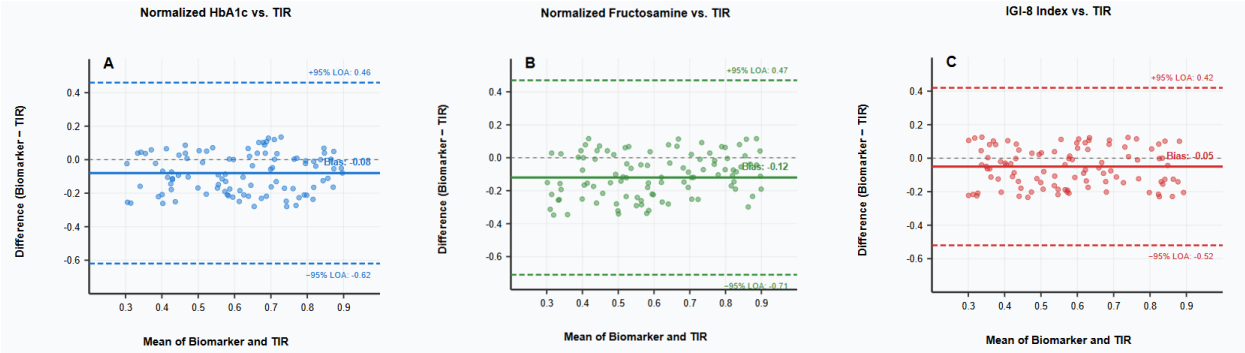
***Clinical Interpretation**: The IGI-8 index effectively stratifies individuals into clinically meaningful glycemic control categories, with each threshold demonstrating clear separation in both HbA1c and mean glucose levels. The excellent control group (IGI-8 < 0.5) maintained near-normoglycemic parameters, while the high risk group (IGI-8 > 1.5) exhibited markedly elevated glycemic markers, underscoring the index's utility for risk assessment and therapeutic decision-making.*

Agreement Analysis Between Normalized Indices and Reference Standards

The agreement between normalized biomarkers and clinically established glycemic targets was evaluated through Bland-Altman analysis. Specifically, when

comparing normalized HbA1c values with the proportion of time during which glycemic outcomes remained within the target range (80–150 mg/dL), obtained through continuous capillary glucose monitoring, a mean bias of –0.08 was observed. The 95% limits of agreement ranged from –0.62 to 0.46, indicating acceptable overall agreement between the two indicators. However, the negative bias suggests a slight tendency for normalized HbA1c to systematically underestimate glycemic burden compared with real-time glucose measurements, which should be considered when interpreting this metric in clinical or research contexts. Similarly, normalized fructosamine, when compared with the same reference, the proportion of time in target glycemic range (80–150 mg/dL) obtained through capillary monitoring, exhibited a mean bias of –0.12, with 95% limits of agreement between –0.71 and 0.47. In turn, the IGI-8 index demonstrated slightly superior agreement, evidenced by an even lower mean bias (–0.05) and narrower 95% limits of agreement (–0.52 to 0.42). The Bland-Altman plots corresponding to these comparisons, illustrated in Figure 3, revealed no systematic patterns of discrepancy across the spectrum of glycemic control evaluated, suggesting that both normalized fructosamine and, particularly, the IGI-8 reflect actual glycemic exposure in individuals in a reasonably balanced manner.

Figure 3. Bland-Altman Analysis of Agreement Between Normalized Glycemic Biomarkers and Time in Range



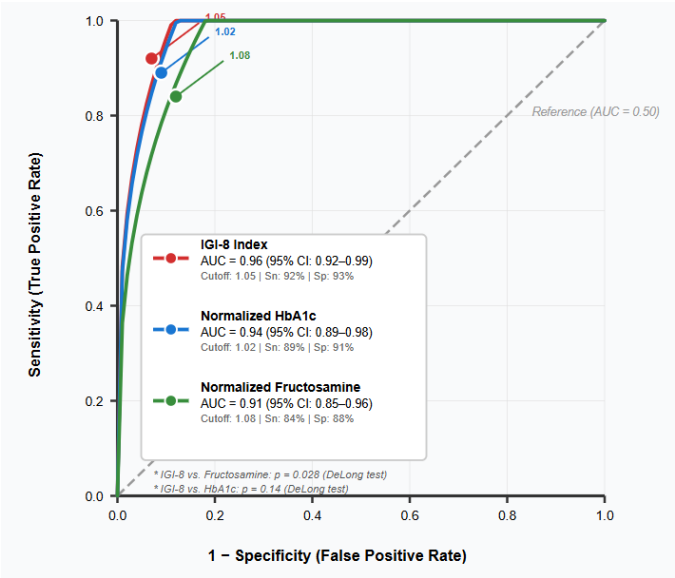
***Clinical Interpretation**: The Bland-Altman analysis confirms that normalized glycemic biomarkers, particularly the IGI-8 index, provide clinically acceptable estimates of glycemic exposure when compared against continuous glucose monitoring. The narrow limits of agreement and minimal systematic bias support their utility in clinical practice and research settings where continuous monitoring may not be feasible. However, caution is warranted regarding the slight tendency toward underestimation when interpreting these metrics in individual patient management.*

Discriminative Performance for Glycemic Control Categories

The discriminative capacity of normalized biomarkers and the IGI-8 index in identifying inadequate glycemic control was evaluated through ROC curve analysis. For operational purposes, glycemic control was considered inadequate when characterized by

HbA1c levels equal to or greater than 7.0% or by a mean capillary glucose equal to or greater than 154 mg/dL, a value corresponding to the estimated glycemic equivalent of an HbA1c of 7.0%. This approach enabled quantification of the diagnostic accuracy of each marker in detecting suboptimal glycemic profiles, aligning with clinical targets widely used in DM management. In the assessment of discriminative capacity for identifying inadequate glycemic control, normalized HbA1c exhibited an area under the ROC curve (AUC) of 0.94 (95% CI: 0.89–0.98), while normalized fructosamine yielded an AUC of 0.91 (95% CI: 0.85–0.96). The composite IGI-8 index demonstrated the strongest performance among the analyzed markers, with an AUC of 0.96 (95% CI: 0.92–0.99). ROC curve comparison tests, utilizing the DeLong method, revealed that the IGI-8 had significantly superior discriminative capacity compared to normalized fructosamine alone ($p = 0.028$). However, although numerically superior, the difference between the IGI-8 and normalized HbA1c did not reach statistical significance ($p = 0.14$), suggesting that both markers offer comparable performance in identifying individuals with decompensated glycemic profiles. Graph 2 presents the ROC curves corresponding to the three evaluated indices, with their respective optimal cutoff points determined based on the balance between sensitivity and specificity. For normalized HbA1c, the ideal cutoff point was identified at 1.02, providing a sensitivity of 89% and specificity of 91%. In the case of normalized fructosamine, the optimal value was 1.08, with a sensitivity of 84% and specificity of 88%. The IGI-8 demonstrated its best performance at a cutoff point of 1.05, achieving a sensitivity of 92% and specificity of 93%, reflecting its high precision in identifying individuals with inadequate glycemic control.

Graph 2. ROC Curves for Detection of Inadequate Glycemic Control

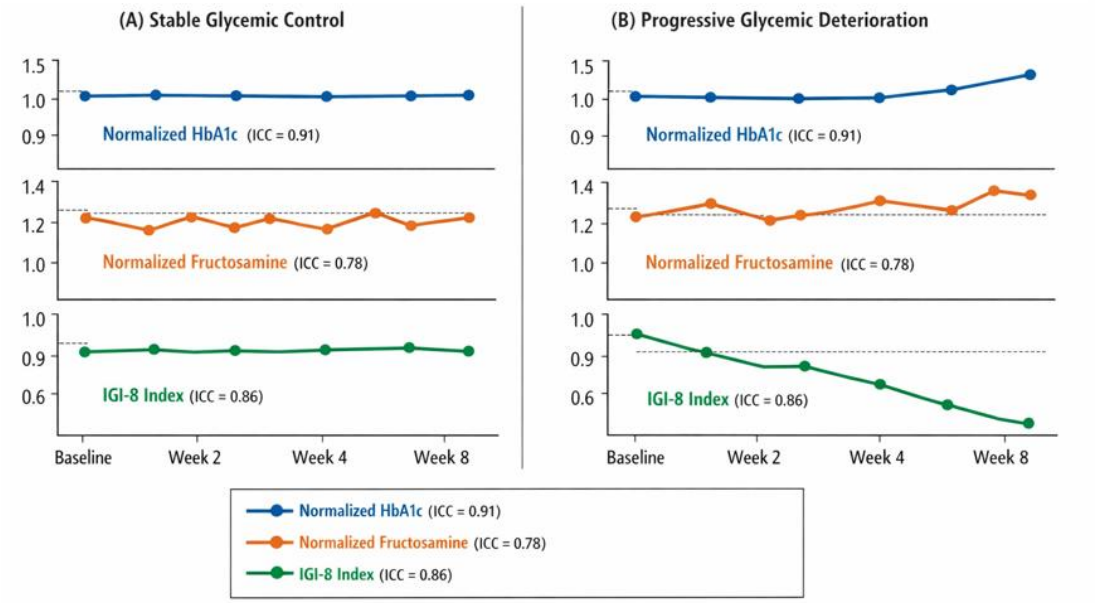


Clinical Interpretation: *All three biomarkers demonstrated excellent discriminative performance (AUC >0.90) for identifying inadequate glycemic control. The IGI-8 index's superior AUC and balanced sensitivity/specificity profile make it particularly suitable for screening and risk stratification. The comparable performance between IGI-8 and normalized HbA1c suggests that both metrics can be used interchangeably in clinical practice. The statistically significant difference between IGI-8 and normalized fructosamine highlights the added value of the composite index approach in capturing multidimensional aspects of glycemic burden.*

Temporal Stability and Reproducibility

Serial laboratory measurements obtained at baseline and at weeks 2, 4, and 8 demonstrated temporal stability of the normalized indices among participants maintained on stable therapeutic regimens (n = 68). The intra-class correlation coefficient (ICC) for normalized HbA1c over the eight-week period was 0.91 (95% CI: 0.87–0.94), indicating excellent reproducibility and temporal consistency. In contrast, normalized fructosamine exhibited greater short-term variability, with an ICC of 0.78 (95% CI: 0.71–0.84), suggesting reduced stability over narrower time windows-likely attributable to its shorter half-life and heightened sensitivity to recent glycemic fluctuations. The IGI-8 displayed intermediate temporal stability, with an ICC of 0.86 (95% CI: 0.81–0.90), aligning with its conceptual design as a biomarker that integrates glycemic information over a time horizon intermediate between that of fructosamine (more responsive to recent glycemic changes) and HbA1c (more reflective of long-term glycemic control). Figure 4 illustrates the longitudinal trajectories of these normalized indices in representative participants, contrasting stable glycemic profiles with those showing progressive deterioration, thereby underscoring the clinical utility of IGI-8 as a balanced indicator of glycemic exposure.

Figure 4. Longitudinal trajectories of normalized glycemic indices



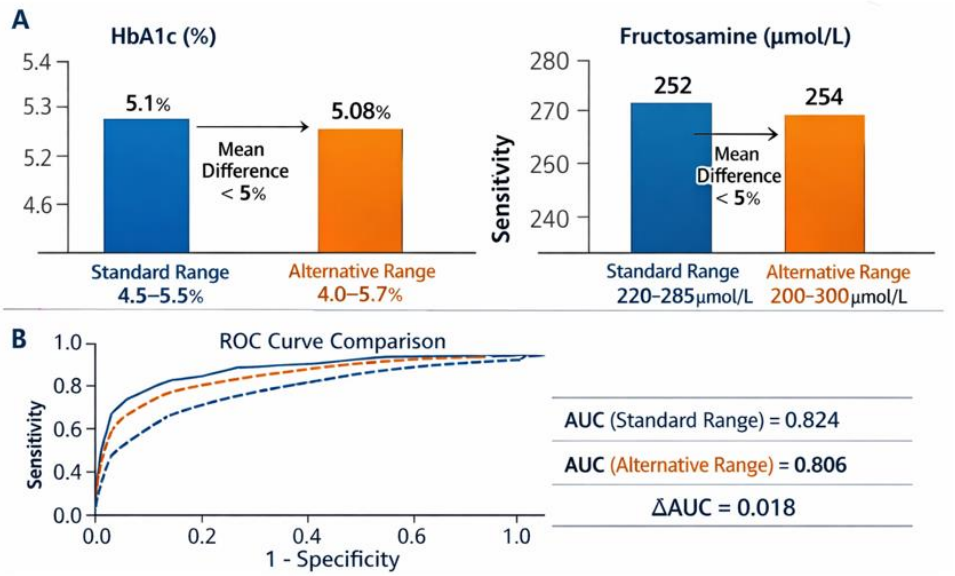
Subgroup Analyses - Diabetes Type

Upon stratification of results by DM type, normalized biomarkers and the 8-point Glycemic Management Index (IGI-8) exhibited comparable performance across both T1DM and T2DM. In T1DM cases (n = 48), a strong positive correlation was observed between IGI-8 and mean capillary glucose (Pearson's r = 0.84, p < 0.001). The discriminative capacity of IGI-8 for identifying inadequate glycemic control was excellent, with a receiver operating characteristic area under the curve (ROC AUC) of 0.95 (95% confidence interval: 0.89–0.99). Similarly, in T2DM cases (n = 52), the correlation between IGI-8 and mean capillary glucose was equally robust (r = 0.80, p < 0.001), with an AUC of 0.96 (95% CI: 0.91–0.99) for detecting suboptimal glycemic control. No statistically significant differences were detected in the discriminative performance of IGI-8 between DM types (p = 0.68), suggesting consistent applicability of this index irrespective of disease etiology.

Methodology Validation through Normalization Sensitivity Analysis

To validate the normalization approach, sensitivity analysis was conducted using alternative reference ranges (HbA1c: 4.0–5.7%; fructosamine: 200–300 µmol/L). This yielded only minimal changes in normalized values (mean difference <5%) without materially impacting the discriminative performance of the indices (AUC difference <0.02), thereby confirming the robustness of the normalization methodology to reasonable variations in reference range selection (Figure 5).

Figure 5. Sensitivity analysis of references ranges



Summary of the Main Results

In summary, normalized HbA1c, normalized fructosamine, and the IGI-8 demonstrated: (1) robust intercorrelations among themselves and with established indicators of glycemic control; (2) high discriminative capacity for identifying inadequate glycemic control, with a slight advantage for the IGI-8; (3) satisfactory agreement with daily capillary glucose monitoring; (4) temporal stability consistent with an intermediate integration window; and (5) consistent performance across DM types and glycemic control categories, with minimal influence from confounding analytical variables.

DISCUSSION

This validation study establishes that standardized glycemic biomarkers can effectively capture intermediate-term glycemic control, addressing an important temporal gap in DM management. The successful normalization of HbA1c and fructosamine into comparable dimensionless scales, combined with their integration into a composite index, demonstrates feasibility for clinical implementation. In this context, our results encourage an objective evaluation of glycemic monitoring, emphasizing the clinical relevance, methodological significance, and potential integration of normalized indices to better reflect dynamic metabolic exposure.

The normalization procedure successfully transformed HbA1c and fructosamine into dimensionless scales with comparable distributions, enabling their mathematical integration. This approach aligns with previous recommendations advocating for standardized biomarker reporting to facilitate clinical interpretation and comparison across different assays.[12,13] The strong correlation observed between normalized HbA1c and normalized fructosamine, despite their distinct temporal windows, is consistent with findings from recent studies demonstrating complementary information provided by these markers when appropriately scaled.[14,15] However, contrary to previous studies that emphasized discordance and the so-called glycation gap, our results suggest that mathematical normalization substantially mitigates this limitation by harmonizing scale and interpretability. This supports the hypothesis that part of the discordance reported in the literature reflects analytical heterogeneity rather than true biological inconsistency.[16]

The development and validation of the composite IGI-8 index represent a pragmatic solution to the gap in medium-term glycemic monitoring, constituting the specific objective of our study. Previous studies have proposed alternative markers, including glycated albumin and metrics derived from continuous glucose monitoring, to

overcome the limitations of isolated laboratory tests.[17,18] However, despite the valuable information provided by these approaches, their applicability is often constrained by cost, accessibility, or biological variability. In contrast, the integrated index described herein leverages widely available assays and demonstrates enhanced discriminatory capacity compared to individual standardized biomarkers, aligning with the broader literature on biomarkers that shows superior performance of composite indices over isolated measures.[19] The weighted integration strategy, which prioritizes the analytical stability of HbA1c while incorporating the short-term responsiveness of fructosamine, aligns with current recommendations for personalized glycemic assessment.[20,21] Our composite approach may prove particularly valuable in clinical contexts requiring timely therapeutic adjustments, where reliance solely on HbA1c may delay recognition of glycemic deterioration.

Recent reviews have highlighted the limitations of isolated biomarker interpretation and emphasized the need for integrated assessment tools.[22] Our findings demonstrate that the mathematical standardization of established biomarkers offers a viable alternative to new assays, potentially facilitating wider implementation without requiring additional laboratory infrastructure. The ideal cut-off points identified for each index provide practical reference values for clinical decision-making, although external validation in diverse populations remains necessary.

The temporal stability analyses in our study demonstrated that the IGI-8 exhibits intermediate reproducibility, positioned between fructosamine and HbA1c, thereby validating its conceptual design as a biomarker reflecting an eight-week glycemic window. This temporal positioning addresses a well-recognized limitation in current monitoring strategies, where the gap between short- and long-term markers complicates therapeutic evaluation.[23] The slightly improved agreement observed with the composite index aligns with evidence indicating that integrated markers more accurately approximate overall glycemic exposure than their individual components.[24]

The agreement analysis demonstrated acceptable concordance between the normalized indices and glucose monitoring metrics, particularly for the IGI-8. Our findings are consistent with the validity of mathematical normalization in preserving physiological correlations with actual glycemic exposure.[25] The slightly improved agreement observed with the IGI-8 aligns with evidence indicating that integrated markers more accurately approximate overall glycemic exposure than their individual components.[26]

Subgroup analyses confirmed consistent performance of the normalized indices in both patients with T1DM and T2DM, suggesting broad applicability irrespective of disease etiology. This applicability across both DM types represents a significant advantage over biomarkers influenced by pathophysiological factors specific to individual forms of DM.[27,28] The substantial discriminative capacity observed in both subgroups supports the potential utility of these indices across diverse clinical populations, although further validation in specific demographic and clinical contexts would strengthen the evidence for widespread implementation.

The sensitivity analysis demonstrated the robustness and statistical relevance of the normalization procedure when subjected to plausible fluctuations in reference interval boundaries, directly addressing potential concerns related to standardization approaches. Nevertheless, this study has limitations, as it relied on secondary laboratory data and did not include prospective follow-up of clinical outcomes, thereby limiting the ability to establish direct associations with adverse complication risk. Despite these constraints, the methodological rigor and consistency with well-established pathophysiological mechanisms in the literature lend strength and credibility to the conclusions.

CONCLUSION

Our findings reinforce the notion that standardized and mathematically normalized glycemic biomarkers provide a coherent and clinically relevant framework for addressing the gap in intermediate-term glycemic assessment. By integrating analytically stable and biologically responsive measures within a composite approach, the IGI-8 index exemplifies how normalization can translate complex glycemic dynamics into actionable clinical information. This strategy not only enhances discriminatory performance compared with isolated biomarkers but also supports more timely and informed therapeutic decision-making in routine DM care. Although the study results offer a robust conceptual and methodological foundation for clinical adoption, external validation and prospective studies remain essential to fully establish the role of these integrated indices in guiding personalized management across diverse diabetic populations.

Conflict of Interest: The authors have no conflict of interest to declare.

REFERENCES

1. Lundholm MD, Emanuele MA, Ashraf A, Nadeem S. Applications and pitfalls of hemoglobin A1C and alternative methods of glycemic monitoring. J Diabetes Complications. 2020;34(8):107585.
2. Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014;37(1):9-16.
3. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.
4. Mattila TK, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. Drugs. 2010;70(17):2229-45.
5. Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, et al. Economic Costs of Diabetes in the U.S. in 2022. Diabetes Care. 2024;47(1):26-43.
6. Azagew AW, Mekonnen CK, Lambie M, Shepherd T, Babatunde OO. Poor glycemic control and its predictors among people living with diabetes in low- and middle-income countries: a systematic review and meta-analysis. BMC Public Health. 2025;25(1):714.
7. Gounden V, Anastasopoulou C, Zubair M, Jialal I. Clinical Utility of Fructosamine and Glycated Albumin. 2025 Sep 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
8. Nayak AU, Holland MR, Macdonald DR, Nevill A, Singh BM. Evidence for consistency of the glycation gap in diabetes. Diabetes Care. 2011;34(8):1712-6.
9. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care. 2003;26(1):163-7.
10. Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014;29(2):388-94.
11. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A View Beyond HbA1c: Role of Continuous Glucose Monitoring. Diabetes Ther. 2019;10(3):853-863.

12. Gillery P. HbA1c and biomarkers of diabetes mellitus in Clinical Chemistry and Laboratory Medicine: ten years after. Clin Chem Lab Med. 2022;61(5):861-872.
13. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Lernmark Å, et al. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. Diabetes Care. 2023;46(10):e151-e199.
14. Toyoshima MTK, Cukier P, Damascena AS, Batista RL, de Azevedo Correa F, Zanatta Kawahara E, et al. Fructosamine and glycated hemoglobin as biomarkers of glycemic control in people with type 2 diabetes mellitus and cancer (GlicoOnco study). Clinics (Sao Paulo). 2023;78:100240.
15. Chandran K, Lee SM, Shen L, Tng EL. Fructosamine and HbA1c: A Correlational Study in a Southeast Asian Population. J ASEAN Fed Endocr Soc. 2024;39(1):26-30.
16. Motshwari DD, George C, Ngwa EN, Zemlin AE, Kengne AP, Davison GM, et al. Are Polymorphisms Within the Fructosamine-3-Kinase Gene Associated With the Discordance Between HbA1c and Other Measures of Glycemia? Diabetes. 2025;74(7):1289-1299.
17. Kaminski CY, Galindo RJ, Navarrete JE, Zabala Z, Moazzami B, Gerges A, et al. Assessment of Glycemic Control by Continuous Glucose Monitoring, Hemoglobin A1c, Fructosamine, and Glycated Albumin in Patients With End-Stage Kidney Disease and Burnt-Out Diabetes. Diabetes Care. 2024;47(2):267-271.
18. Desouza CV, Rosenstock J, Kohzuma T, Fonseca VA. Glycated Albumin Correlates With Time-in-Range Better Than HbA1c or Fructosamine. J Clin Endocrinol Metab. 2023;108(11):e1193-e1198.
19. Sun A, Li Y, Zhou XH. Biomarker Combination Based on the Youden Index With and Without Gold Standard. Stat Med. 2025;44(18-19):e70189.
20. Dunn TC, Xu Y, Bergenstal RM, Ogawa W, Ajjan RA. Personalized Glycated Hemoglobin in Diabetes Management: Closing the Gap with Glucose Management Indicator. Diabetes Technol Ther. 2023;25(S3):S65-S74.
21. Krhač M, Lovrenčić MV. Update on biomarkers of glycemic control. World J Diabetes. 2019;10(1):1-15.
22. Xiong JY, Wang JM, Zhao XL, Yang C, Jiang XS, Chen YM, et al. Glycated albumin as a biomarker for diagnosis of diabetes mellitus: A systematic review and meta-analysis. World J Clin Cases. 2021;9(31):9520-9534.

23. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technol Ther. 2019;21(2):81-85.
24. Nguyen M, Han J, Spanakis EK, Kovatchev BP, Klonoff DC. A Review of Continuous Glucose Monitoring-Based Composite Metrics for Glycemic Control. Diabetes Technol Ther. 2020;22(8):613-622.
25. Daya NR, Fang M, Shin JI, Pankow JS, Lutsey PL, Valint A, et al. Detecting Hyperglycemia Using Biomarkers Versus Continuous Glucose Monitoring. Diabetes Care. 2025;48(8):1446-1452.
26. Kodama S, Yamada T, Yagyuda N, Tanaka N, Wu S, Ferreira ED, et al. Comparison of the ability to diagnose gestational diabetes mellitus between glycated albumin or fructosamine and hemoglobin A1c-a meta-analysis of diagnostic studies. Syst Rev. 2025;14(1):144.
27. Al-Lahham Y, Volanski W, Signorini L, Prado ALD, Valdameri G, Moure VR, et al. Reference Interval for Glycated Albumin, 1,5-AG/GA, and GA/HbA1c Ratios and Cut-Off Values for Type 1, Type 2, and Gestational Diabetes: A Cross-Sectional Study. Biomedicines. 2024;12(12):2651. Erratum in: Biomedicines. 2025;13(7):1621.
28. Lenters-Westra E, Atkin SL, Kilpatrick ES, Slingerland RJ, Sato A, English E. Limitations of glycated albumin standardization when applied to the assessment of diabetes patients. Clin Chem Lab Med. 2024;62(12):2526-2533.

This preprint was submitted under the following conditions:

- The authors declare that the necessary Terms of Free and Informed Consent of participants or patients in the research were obtained and are described in the manuscript, when applicable.
- The authors declare that the preparation of the manuscript followed the ethical norms of scientific communication.
- The authors declare that they are aware that they are solely responsible for the content of the preprint and that the deposit in SciELO Preprints does not mean any commitment on the part of SciELO, except its preservation and dissemination.
- The authors declare that the data, applications, and other content underlying the manuscript are referenced.
- The deposited manuscript is in PDF format.
- The authors declare that the research that originated the manuscript followed good ethical practices and that the necessary approvals from research ethics committees, when applicable, are described in the manuscript.
- The authors declare that once a manuscript is posted on the SciELO Preprints server, it can only be taken down on request to the SciELO Preprints server Editorial Secretariat, who will post a retraction notice in its place.
- The authors agree that the approved manuscript will be made available under a Creative Commons CC-BY license.
- The submitting author declares that the contributions of all authors and conflict of interest statement are included explicitly and in specific sections of the manuscript.
- The authors declare that the manuscript was not deposited and/or previously made available on another preprint server or published by a journal.
- If the manuscript is being reviewed or being prepared for publishing but not yet published by a journal, the authors declare that they have received authorization from the journal to make this deposit.
- The submitting author declares that all authors of the manuscript agree with the submission to SciELO Preprints.