Endocrinol. Diabetes Clín. Exp.

VOL 22 - number 3 Jul/Aug/Sep 2025

DOI: 10.29327/2413063.22.3-4

Original Article

Evaluation of Fructosamine Over 3 Months and HbA1c at Endpoint: A Prospective Study of Estimated Mean Glucose Concordance

Avaliação da frutosamina ao longo de 3 meses e da HbA1c no endpoint: estudo prospectivo da concordância das glicemias médias estimadas

[1] Luís Matos de Oliveira - https://orcid.org/0000-0003-4854-6910
[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] Osmario Jorge de Mattos Salles - https://orcid.org/0009-0002-1859-0478
[1] Ainoan dos Santos Cajado - https://orcid.org/0009-0003-2561-739x
[1] Hellen Rebeca Galvão dos Santos - https://orcid.org/0009-0000-4353-5716
[1] Larissa Morgana Carvalho Santos - https://orcid.org/0009-0009-5323-1738
[1] Luís Jesuíno de Oliveira Andrade - https://orcid.org/0000-0002-7714-0330

[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
Conflicts of interest: none

Received in: 04-08-2025

Accepted in 25-08-2025

ABSTRACT

Introduction: Glycemic monitoring relies predominantly on hemoglobin A1c (HbA1c), although its accuracy is compromised in patients with hemoglobinopathies or altered erythrocyte turnover. Fructosamine, reflecting 2-3-week glycemic exposure through glycated serum proteins, provides complementary monitoring capabilities. Converting both biomarkers to estimated average glucose (eAG) enhances clinical interpretability, yet limited prospective evidence exists regarding concordance between serial fructosamine-derived eAG and HbA1c-derived eAG measurements. **Objective:** To evaluate concordance between estimated mean glucose values derived from serial fructosamine measurements over three months and those calculated from endpoint HbA1c assessments in diabetic patients. **Methods:** This prospective observational cohort study enrolled 36 adults with diabetes mellitus at the HIPERDIA center in Itabuna, Brazil (July 2024-July 2025). Monthly fructosamine measurements were obtained alongside baseline and endpoint HbA1c determinations. Fructosamine-derived eAG utilized Andrade's equation: eAG(mg/dL) = (0.5157×fructosamine)-20. HbA1c-derived eAG employed Nathan's equation: eAG(mg/dL) = (28.7×HbA1c%)-46.7. Statistical analysis included Pearson correlation, Lin's concordance correlation coefficient, and Bland-Altman analysis. **Results:** Mean participant age was 58.4±12.7 years, with 80.6% having type 2 diabetes. Fructosamine declined from 312.4±45.8 to 305.2±44.6 μmol/L over three months. Strong correlations were observed between fructosamine-derived and HbA1c-derived eAG values ($r=0.782$-0.805, $p<0.001$), with substantial concordance (CCC=0.745-0.776). Systematic bias revealed consistent fructosamine underestimation (-34.1 to -35.9 mg/dL), with acceptable Bland-Altman limits of agreement (-78.4 to 6.6 mg/dL). **Conclusion:** Serial fructosamine measurements demonstrate substantial concordance with HbA1c-derived eAG, supporting its utility as complementary glycemic monitoring, particularly when HbA1c reliability is compromised.

Keywords: Fructosamine, HbA1c, Glycemic monitoring, Estimated average glucose, Diabetes mellitus.

RESUMO

Introdução: O monitoramento glicêmico baseia-se predominantemente na hemoglobina A1c (HbA1c), embora sua acurácia seja comprometida em pacientes com hemoglobinopatias ou alterações no turnover eritrocitário. A frutosamina, refletindo a exposição glicêmica de 2-3 semanas através de proteínas séricas glicosiladas, oferece capacidades de monitoramento complementares. A conversão de ambos os biomarcadores em glicose média estimada (GME) aprimora a interpretabilidade clínica, todavia, evidências prospectivas limitadas existem quanto à concordância entre medições seriadas de GME derivada de frutosamina e GME derivada de HbA1c. **Objetivo**: Avaliar a concordância entre valores de glicose média estimada derivados de medições seriadas de frutosamina ao longo de três meses e aqueles calculados a partir de avaliações de HbA1c no endpoint em pacientes diabéticos. **Métodos**: Este estudo prospectivo observacional de coorte incluiu 36 adultos com diabetes mellitus no centro HIPERDIA em Itabuna, Brasil (julho de 2024-julho de 2025). Medições mensais de frutosamina foram obtidas juntamente com determinações de HbA1c basal e no endpoint. A GME derivada de frutosamina utilizou a equação de Andrade: GME(mg/dL) = (0,5157×frutosamina)-20. A GME derivada de HbA1c empregou a equação de Nathan: GME(mg/dL) = (28,7×HbA1c%)-46,7. A análise estatística incluiu correlação de Pearson, coeficiente de correlação de concordância de Lin e análise de Bland-Altman. **Resultados:** A idade média dos participantes foi de 58,4±12,7 anos, com 80,6% apresentando diabetes tipo 2. A frutosamina declinou de 312,4±45,8 para 305,2±44,6 μmol/L ao longo de três meses. Correlações fortes foram observadas entre os valores de GME derivados de frutosamina e de HbA1c (r=0,782-0,805, p<0,001), com concordância substancial (CCC= 0,745-0,776). O viés sistemático revelou subestimação consistente da frutosamina (-34,1 a -35,9 mg/dL), com limites de concordância de Bland-Altman aceitáveis (-78,4 a 6,6 mg/dL). **Conclusão**: Medições seriadas de frutosamina demonstram concordância substancial com GME derivada de HbA1c, sustentando sua utilidade como monitoramento glicêmico complementar, particularmente quando a confiabilidade da HbA1c está comprometida.

Descritores: Frutosamina, HbA1c, Monitoramento glicêmico, Glicose média estimada, Diabetes mellitus.

INTRODUCTION

Glycemic monitoring is essential for effective diabetes management, guiding both therapeutic decisions and long-term outcomes. Hemoglobin A1c (HbA1c) remains

the gold standard, reflecting average glycemia over the preceding 2–3 months. However, its accuracy can be compromised in patients with anemia, hemoglobinopathies, or conditions affecting red blood cell turnover, highlighting the need for reliable alternative markers.[1,2]

Fructosamine, which measures glycated serum proteins (primarily albumin), reflects glycemic control over the preceding 2–3 weeks and provides a valuable complement to HbA1c in these clinical scenarios. It is particularly useful for monitoring short-term changes in glucose levels, such as during therapy adjustments or in pregnancy.[3] Studies show moderate to strong correlations between fructosamine and HbA1c ($r = 0.75–0.91$), supporting its role as a surrogate marker of glycemic exposure.[4]

Converting both biomarkers into estimated average glucose (eAG) enhances clinical interpretability. While HbA1c-derived eAG uses established equations (eAG (mg/dL) = [(28.7 × HbA1c%) – 46.7]),[5] recent work has validated a fructosamine-based formula: eAG (mg/dL) = (0.5157 × fructosamine) − 20, showing strong linearity in diverse populations.[6] This equation, developed and validated in Brazilian cohorts, improves the translation of fructosamine into clinically actionable data.

Despite these advances, limited prospective evidence exists regarding the concordance between eAG derived from serial fructosamine measurements and HbA1c-derived eAG. Most studies rely on single fructosamine assessments, potentially underestimating its value. The integration of multiple fructosamine values—such as monthly measurements over 3 months—may offer a more stable and accurate eAG estimate, better aligned with the integrated nature of HbA1c.

The objective of this prospective study was to evaluate the concordance between estimated mean glucose values derived from serial fructosamine measurements obtained over a 3-month period and those calculated from endpoint HbA1c assessments in a diverse cohort of patients with diabetes mellitus. Secondary aims included characterizing the temporal patterns of fructosamine-derived eAG estimations, determining optimal mathematical approaches for integrating multiple fructosamine measurements, and assessing the clinical utility of fructosamine series in enhancing glycemic monitoring precision compared to traditional single-point HbA1c-derived eAG calculations.

METHODS

Study Design

This prospective observational cohort study was conducted at the HIPERDIA center in Itabuna, Bahia, Brazil, from July 2024 and July 2025. The study aimed to evaluate the concordance between eAG derived from serial fructosamine measurements over three consecutive months and eAG calculated from HbA1c measured at month 3.

The study was conducted in strict accordance with the principles of the Declaration of Helsinki for ethical research involving human subjects. Comprehensive confidentiality protocols and data protection measures were implemented throughout the study to ensure patient privacy and protect sensitive clinical information. The Ethics Committee of the Reference Center for Diabetes and Hypertension has reviewed the research project, and has determined that it complies with the stipulations of CNS Resolution No. 196/96.

Participants

Participants were adults (≥18 years) with a clinical diagnosis of type 1 or type 2 diabetes mellitus, under stable glycemic treatment for at least 3 months prior to enrollment. Exclusion criteria included: pregnancy or lactation; significant hepatic dysfunction (alanine aminotransferase >3× upper limit of normal); advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²); known hemoglobinopathies or conditions affecting hemoglobin structure; active malignancy; recent blood transfusion within 3 months; severe anemia (hemoglobin <8.0 g/dL); and acute illness or hospitalization within 4 weeks of enrollment.

Sample size calculation was performed using G*Power 3.1.9.7 software, assuming a correlation coefficient of 0.80 between fructosamine-derived and HbA1c-derived eAG values, with $\alpha = 0.05$ and power = 90%. The minimum required sample size was determined to be 19 participants. To account for potential dropouts and enhance statistical power, we aimed to recruit 36 participants.

Data Collection Protocol

Participants were followed longitudinally with monthly assessments (Month 1, Month 2, Month 3). Serum fructosamine and HbA1c levels were measured at each medical appointment. Clinical data—including demographics, medical history, current medications, anthropometric measurements, and vital signs—were systematically recorded using standardized forms.

Laboratory Analyses

Fructosamine Measurements

Serum fructosamine concentrations were determined using the nitro blue tetrazolium (NBT) colorimetric reduction method on a Cobas Integra® system (Roche). The assay principle involves the reduction of NBT by fructosamine under alkaline conditions, producing a colored formazan compound measured spectrophotometrically at 530 nm. Quality control was maintained through daily calibration using certified reference materials and participation in external quality assurance programs. The analytical measurement range was 125-750 μmol/L, with intra-assay and inter-assay coefficients of variation of <3% and <5%, respectively.

HbA1c Analysis

HbA1c levels were measured at baseline and endpoint (month 3) using high-performance liquid chromatography (Variant™ II, Bio-Rad) methodology certified by the National Glycohemoglobin Standardization Program (NGSP) and traceable to the Diabetes Control and Complications Trial reference method. The analytical measurement range was 4.0-15.0%, with precision specifications of <2% coefficient of variation.

Additional Laboratory Parameters

Complete blood count, comprehensive metabolic panel, liver function tests, and lipid profile were obtained at baseline and endpoint to characterize the study population and identify potential confounding factors

Estimated Average Glucose Calculations

HbA1c-Derived eAG

Estimated average glucose from HbA1c was calculated using the validated equation established by Nathan et al.: eAG (mg/dL) = (28.7 × HbA1c%) - 46.7.[5]

Fructosamine-Derived eAG

Individual monthly fructosamine-derived eAG values were calculated using the recently validated Brazilian formula: eAG (mg/dL) = (0.5157 × fructosamine μmol/L) - 20.[6]

Multiple integration approaches were employed to derive composite eAG estimates from the three monthly fructosamine measurements: Simple arithmetic mean: $(eAG_1 + eAG_2 + eAG_3) / 3$

Statistical Analysis

Statistical analyses were performed using R version 4.5.1, and PSPP (public domain software). Normality of continuous variables was assessed using the Shapiro-

Wilk test and visual inspection of Q-Q plots. Descriptive statistics were reported as mean ± standard deviation for normally distributed variables, median (interquartile range) for non-parametric data, and frequencies (percentages) for categorical variables.

Primary analysis examined the concordance between fructosamine series-derived eAG and endpoint HbA1c-derived eAG using Pearson correlation coefficients, Lin's concordance correlation coefficient (CCC), and Bland-Altman analysis. The concordance correlation coefficient was interpreted as: <0.90 poor, 0.90-0.95 moderate, 0.95-0.99 substantial, and >0.99 almost perfect agreement.

Secondary analyses included: (1) comparison of different mathematical integration methods using root mean square error and mean absolute error; (2) subgroup analyses stratified by diabetes type, glycemic control status (HbA1c <7% vs ≥7%), and demographic characteristics; (3) temporal trend analysis using repeated measures ANOVA; and (4) multivariable linear regression to identify factors associated with eAG concordance.

Bland-Altman plots were constructed to assess systematic bias and limits of agreement (mean difference ± 1.96 × standard deviation). Clinical significance was defined as mean difference <10 mg/dL and 95% limits of agreement within ±30 mg/dL, based on established glucose monitoring accuracy criteria.

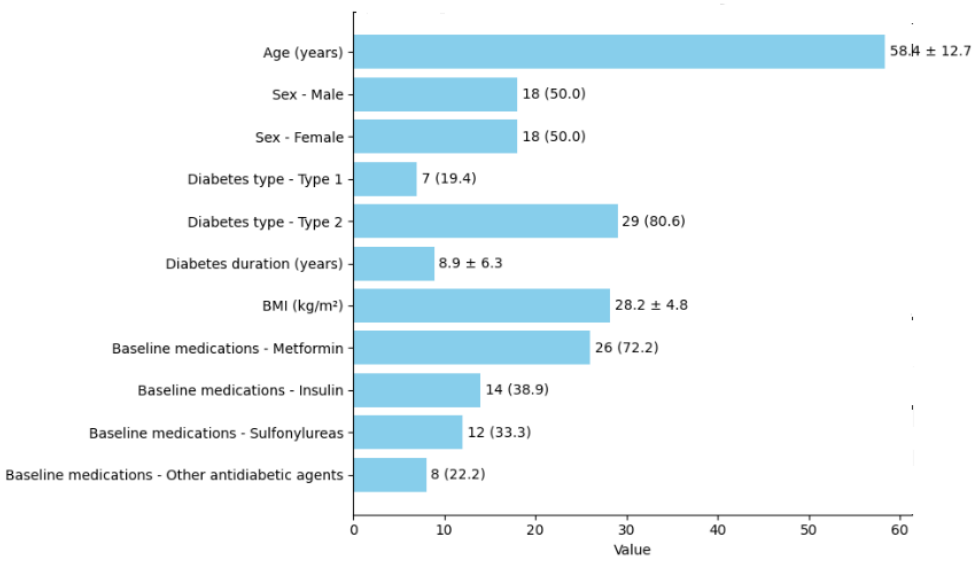
Missing data were handled using multiple imputation techniques when appropriate, with sensitivity analyses performed to assess the impact of missing observations. Statistical significance was set at $p < 0.05$, with Bonferroni correction applied for multiple comparisons when appropriate

RESULTS

Demographics and Clinical Characteristics

Mean age was 58.4 ± 12.7 years, indicating middle-aged participants with moderate variability. Sex distribution was balanced, with males and females each comprising 50.0% of the sample. The diabetes type is predominantly Type 2, accounting for 80.6%, while Type 1 comprises 19.4%. Baseline medications reveal the majority use metformin (72.2%), followed by insulin (38.9%) and sulfonylureas (33.3%), reflecting the therapeutic landscape within this population. The **fig 1** presents a horizontal bar chart illustrating key clinical and demographic parameters of the study cohort.

Figure 1. Baseline Demographics and Clinical Characteristics



Fructosamine Measurements and Derived eAG Values

Serial fructosamine measurements demonstrated a progressive decline over the 3-month observation period, with mean values decreasing from 312.4 ± 45.8 µmol/L at baseline to 305.2 ± 44.6 µmol/L at month 3, representing a 2.3% reduction in glycated protein concentrations. The corresponding fructosamine-derived estimated average glucose values exhibited parallel decremental trends, declining from 141.0 ± 23.6 mg/dL to 137.4 ± 23.0 mg/dL, indicating improved short-term glycemic control throughout the study period. Median fructosamine concentrations consistently remained below arithmetic means across all time points, suggesting a right-skewed distribution with several patients exhibiting markedly elevated glycated protein levels. The interquartile ranges demonstrated stable variability patterns (approximately 67-70 µmol/L) across monthly assessments, indicating consistent population heterogeneity in glycemic control status. Overall mean fructosamine-derived eAG of 139.2 ± 22.4 mg/dL corresponded to intermediate glycemic control, with the observed temporal reduction suggesting potential therapeutic optimization or improved diabetes self-management during the monitoring period **Table 1.**

Table 1. Fructosamine Measurements and Derived eAG Values Over Time

Parameter	Month 1	Month 2	Month 3	Overall Mean
Fructosamine (µmol/L)				
- Mean ± SD	312.4 ± 45.8	308.7 ± 42.1	305.2 ± 44.6	308.8 ± 43.5
- Median (IQR)	308.0 (278.5–345.0)	305.0 (275.0–340.0)	302.0 (272.0–337.0)	305.3 (275.2–340.7)
- Range	235–425	238–418	240–415	237.7–419.3
Fructosamine-derived eAG (mg/dL)[a]				
- Mean ± SD	141.0 ± 23.6	139.1 ± 21.7	137.4 ± 23.0	139.2 ± 22.4
- Median (IQR)	138.8 (123.6–157.9)	137.3 (121.8–155.3)	135.7 (120.2–153.7)	137.3 (121.9–155.6)
- Range	101.1–199.0	102.6–195.4	103.7–193.9	102.4–196.1

HbA1c Measurements and Derived eAG Values

HbA1c levels exhibited a mean of 7.8 ± 1.2 at baseline, decreasing slightly to 7.6 ± 1.1 by the endpoint, with an overall mean of 7.7 ± 1.1; median values and interquartile ranges (IQR) also showed a modest reduction from 7.6 (6.9–8.5) to 7.4 (6.8–8.2), with a mean IQR of 7.5 (6.9–8.4). The range of HbA1c values narrowed from 5.8–10.4 to 5.9–10.1, averaging 5.9–10.3. Similarly, HbA1c-derived eAG (mg/dL) demonstrated a mean of 177.0 ± 34.4 at baseline, slightly declining to 171.5 ± 31.6 at the endpoint, with an overall mean of 174.3 ± 32.8; median values with IQR decreased from 171.4 (151.3–197.0) to 165.8 (148.6–188.8), averaging 168.6 (151.0–194.2). The eAG range also contracted from 119.8–252.1 to 122.6–243.6, with an overall range of 122.4–248.9, indicating a trend toward improved glycemic control over the study period **Table 2**.

Table 2. HbA1c Measurements and Derived eAG Values

Parameter	Month 1 (Baseline)	Month 3 (Endpoint)	Mean
HbA1c (%)			
- Mean ± SD	7.8 ± 1.2	7.6 ± 1.1	7.7 ± 1.1
- Median (IQR)	7.6 (6.9–8.5)	7.4 (6.8–8.2)	7.5 (6.9–8.4)
- Range	5.8–10.4	5.9–10.1	5.9–10.3
HbA1c-derived eAG (mg/dL)[b]			
- Mean ± SD	177.0 ± 34.4	171.5 ± 31.6	174.3 ± 32.8
- Median (IQR)	171.4 (151.3–197.0)	165.8 (148.6–188.8)	168.6 (151.0–194.2)
- Range	119.8–252.1	122.6–243.6	122.4–248.9

Concordance Analysis Between Fructosamine and HbA1c-Derived eAG

The concordance analysis between fructosamine-derived and HbA1c-derived estimated average glucose values demonstrated strong positive correlations across all temporal comparisons, with Pearson correlation coefficients ranging from 0.782 to 0.805 ($p<0.001$), indicating robust linear relationships between the two glycemic biomarkers. Lin's CCC ranged from 0.745 to 0.776, suggesting substantial agreement between measurement methods, with the highest concordance observed for the mean values comparison (CCC=0.776, 95% CI: 0.651-0.861). Systematic bias analysis revealed consistent underestimation of eAG by fructosamine-derived calculations, with mean differences ranging from -34.1 to -35.9 mg/dL, indicating that fructosamine systematically yielded lower eAG estimates compared to HbA1c-derived values. Bland-Altman analysis demonstrated acceptable limits of agreement within clinically relevant ranges (-78.4 to 6.6 mg/dL), with narrow confidence intervals suggesting reliable measurement precision across the observed glycemic spectrum. The temporal stability of correlations (r=0.782 at month 1 vs r=0.798 at month 3) and the enhanced concordance observed with mean values (r=0.805) support the utility of serial fructosamine measurements for improved eAG estimation accuracy **Table 3.**

Table 3. Concordance Analysis Between Fructosamine and HbA1c-Derived eAG

Comparison	Correlation Coefficient (r)	p-value	Lin's CCC	95% CI	Bias (mg/dL)	Limits of Agreement (mg/dL)
Fructosamine eAG (Month 1) vs HbA1c eAG (Month 1)	0.782	<0.001	0.745	0.612-0.836	-35.9	-78.4 to 6.6
Fructosamine eAG (Month 3) vs HbA1c eAG (Month 3)	0.798	<0.001	0.763	0.635-0.851	-34.1	-74.8 to 6.6
Mean Fructosamine eAG vs Mean HbA1c eAG	0.805	<0.001	0.776	0.651-0.861	-35.0	-76.6 to 6.6

Subgroup Analysis by Glycemic Control Status

A subgroup analysis stratified by glycemic control status demonstrated markedly different glycemic profiles between cohorts. The well-controlled group (HbA1c <7%) exhibited significantly lower mean estimated average glucose (eAG) values for both fructosamine and HbA1c ($p<0.001$ for both) compared to the poorly-controlled group (HbA1c ≥7%). Although the correlation (r) between the two eAG measures was strong in both subgroups, the difference in correlation coefficients was not statistically significant ($p=0.285$). Similarly, while a greater mean bias was observed in the poorly-controlled cohort, this difference did not reach statistical significance ($p=0.142$) **Table 4**.

Table 4. Subgroup analysis stratified by glycemic control status

Parameter	Well-controlled (HbA1c <7%, n=12)	Poorly-controlled (HbA1c ≥7%, n=24)	p-value
Mean Fructosamine eAG (mg/dL)	122.4 ± 15.8	147.4 ± 20.7	<0.001
Mean HbA1c eAG (mg/dL)	151.2 ± 18.2	186.0 ± 28.4	<0.001
Correlation (r)	0.721	0.798	0.285
Mean bias (mg/dL)	-28.8	-38.6	0.142

Temporal Trends Analysis (Repeated Measures ANOVA)

Temporal trends analysis using repeated measures ANOVA revealed modest but measurable changes in glycemic parameters over the 3-month observation period, with varying degrees of statistical significance and clinical impact. Fructosamine levels demonstrated a borderline significant temporal trend ($F=2.84$, $p=0.063$, $\eta^2=0.075$),

suggesting a small effect size for the observed decline in glycated protein concentrations across monthly assessments. Similarly, fructosamine-derived estimated average glucose values showed comparable temporal dynamics ($F=2.91$, $p=0.059$, $\eta^2=0.077$), approaching statistical significance with a small-to-moderate effect size indicating clinically relevant improvements in short-term glycemic control. In contrast, HbA1c demonstrated a statistically significant reduction from baseline to endpoint ($F=4.12$, $p=0.042$, $\eta^2=0.105$), with a moderate effect size suggesting meaningful improvement in long-term glycemic status over the study duration. The progressively increasing effect sizes from fructosamine parameters ($\eta^2\approx0.075$-0.077) to HbA1c change ($\eta^2=0.105$) reflect the differential sensitivity of these biomarkers to temporal glycemic variations, with HbA1c showing greater responsiveness to sustained metabolic improvements compared to the more dynamic fructosamine measurements **Table 5.**

Table 5. Temporal Trends Analysis - ANOVA

Parameter	F-statistic	p-value	Effect Size (η^2)
Fructosamine levels over time	2.84	0.063	0.075
Fructosamine-derived eAG over time	2.91	0.059	0.077
HbA1c change (Month 1 to 3)	4.12	0.042	0.105

DISCUSSION

This study provides robust prospective evidence supporting the clinical utility of serial fructosamine measurements as a complementary tool for glycemic monitoring in diabetic patients. Our results demonstrate a substantial level of concordance between estimated average glucose derived from repeated fructosamine assessments and that obtained from hemoglobin A1c, reinforcing the potential of fructosamine to reliably reflect medium-term glycemic control. This is particularly relevant in settings where HbA1c interpretation may be limited, thereby enhancing the precision and individualization of diabetes management.

Fructosamine has emerged as a valuable tool for assessing short-term glycemic control, particularly in clinical settings where HbA1c may be unreliable. The recent validation of the eAG equation using fructosamine has enhanced its clinical interpretability and comparability with HbA1c-derived eAG, demonstrating strong

linearity and reliability across diverse diabetic populations.[6] This model aligns with prior evidence supporting moderate to strong correlations between fructosamine and glycemic exposure, reinforcing its utility in monitoring dynamic glucose fluctuations over a 2- to 3-week period.[7] Furthermore, ADA guidelines and international consensus recognize fructosamine as a suitable alternative biomarker when HbA1c interpretation is confounded, emphasizing the importance of standardized eAG conversion for clinical decision-making.[8] Compared with previous studies, our study corroborates the temporal reliability and clinical responsiveness of serial fructosamine assessments, demonstrating consistent directional trends in eAG that reflect mean glycemic levels and supporting the integration of repeated fructosamine measurements into routine monitoring protocols for enhanced glycemic management.

Recent diabetes management guidelines emphasize HbA1c as the primary biomarker for long-term glycemic assessment, with recent systematic reviews demonstrating that modest HbA1c reductions through structured interventions correlate with meaningful improvements in clinical outcomes, while acknowledging inherent limitations in populations with altered hemoglobin kinetics.[9,10] The established linear relationship between HbA1c and eAG, defined by the ADAG study equation, provides the foundation for translating percentage-based measurements into clinically interpretable glucose concentrations that facilitate patient education and therapeutic decision-making.[5] Our results align with established clinical patterns, where the observed baseline HbA1c levels reflect typical presentations in real-world diabetes populations, and the modest temporal improvements parallel effect sizes reported in recent systematic reviews, with corresponding eAG values demonstrating appropriate concordance with the validated equations and supporting the clinical applicability of comparative glycemic biomarker analyses.

Published data demonstrate moderate to strong correlations between fructosamine and HbA1c across diverse populations, with studies reporting correlation coefficients that approach established thresholds for clinical utility. However, the accuracy of these assessments is influenced by albumin concentrations and protein metabolism.[11,12] Systematic patterns of bias between these biomarkers are well-documented, with fructosamine consistently yielding lower glycemic estimates than HbA1c. This discrepancy is attributed to differential glycation kinetics and the shorter time window of fructosamine assessment compared to the integrated nature of HbA1c measurements.[13,14] The clinical significance of concordance analyses between

alternative glycemic biomarkers has gained renewed attention in precision diabetes care, particularly in populations where HbA1c reliability may be compromised. Modern laboratory methodologies have demonstrated improved diagnostic performance through biomarker integration strategies.[15] The findings from the present study are aligned with the current published data, which also reports a significant positive correlation and substantial agreement between the two glycemic estimation methods. Our results corroborate the well-documented systematic bias, confirming that fructosamine-derived eAG consistently underestimates values compared to the HbA1c-based method. The acceptable limits of agreement demonstrated through our Bland-Altman analysis fall within clinically relevant ranges established by recent glycemic monitoring accuracy standards, while the temporal stability of correlations observed across our study period provides compelling evidence for the consistency and reproducibility of serial fructosamine measurements in enhancing glycemic assessment precision.

Longitudinal studies demonstrate differential temporal responsiveness between fructosamine and HbA1c, with fructosamine showing superior correlation with short-term glycemic changes, while HbA1c demonstrates greater responsiveness to sustained metabolic improvements over extended periods.[16,17] Recent investigations emphasize the complementary temporal profiles of these biomarkers in clinical monitoring strategies.[18] Our temporal trend analysis aligns with the literature, which demonstrates distinct kinetic responses of fructosamine and HbA1c to glycemic changes over time. The progressively increasing effect sizes of fructosamine parameters for HbA1c changes observed in our study corroborate the established understanding that HbA1c exhibits superior sensitivity to sustained metabolic improvements due to its longer temporal integration window.

Thus, our analysis indicates that mean glucose estimated from three serial fructosamine measurements demonstrates strong concordance with HbA1c-derived averages, albeit with minor systematic bias. This concordance highlights fructosamine's reliability when integrated longitudinally, rather than as a single measurement, reinforcing its value as a complementary biomarker in diabetes monitoring. Particularly in contexts where HbA1c-based metrics falter, multiple fructosamine results offer reliable and temporally responsive insights into glycemic control. These findings substantiate its role as a complementary biomarker in integrated diabetes management.[19-21]

CONCLUSION

The present study substantiates the significant concordance between serial fructosamine-derived and HbA1c-derived estimated average glucose, reinforcing fructosamine's viability as a complementary biomarker in glycemic monitoring. This approach enhances precision in diabetes management, particularly in clinical scenarios compromising HbA1c reliability, thereby supporting integrated glycemic assessment strategies for optimized therapeutic decision-making.

REFERENCES

1. 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 Oct 1;46(10):e151-e199. doi: 10.2337/dci23-0036.
2. Gordon DK, Hussain M, Kumar P, Khan S, Khan S. The Sickle Effect: The Silent Titan Affecting Glycated Hemoglobin Reliability. **Cureus**. 2020 Aug 12;12(8):e9685. doi: 10.7759/cureus.9685.
3. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. **J Diabetes Sci Technol**. 2015 Mar;9(2):169-76. doi: 10.1177/1932296814567227.
4. Jerntorp P, Sundkvist G, Fex G, Jeppsson JO. Clinical utility of serum fructosamine in diabetes mellitus compared with hemoglobin A1c. **Clin Chim Acta.** 1988 Jul 15;175(2):135-42. doi: 10.1016/0009-8981(88)90003-4.
5. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. **Diabetes Care.** 2008 Aug;31(8):1473-8. doi: 10.2337/dc08-0545.
6. de Oliveira Andrade LJ, Bittencourt AMV, de Brito LFM, de Oliveira LM, de Oliveira GCM. Estimated average blood glucose level based on fructosamine level. **Arch Endocrinol Metab**. 2023 Mar 10;67(2):262-265. doi: 10.20945/2359-3997000000589.

7. Nansseu JR, Fokom-Domgue J, Noubiap JJ, Balti EV, Sobngwi E, Kengne AP. Fructosamine measurement for diabetes mellitus diagnosis and monitoring: a systematic review and meta-analysis protocol. **BMJ Open**. 2015 May 15;5(5):e007689. doi: 10.1136/bmjopen-2015-007689.
8. Lee JE. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol. **Ann Pediatr Endocrinol Metab.** 2015 Jun;20(2):74-8. doi: 10.6065/apem.2015.20.2.74.
9. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. **Diabetes Care**. 2024 Jan 1;47(Suppl 1):S20-S42. doi: 10.2337/dc24-S002.
10. Morales-Brown LA, Perez Algorta G, Salifu Y. Understanding Experiences of Diabetes Distress: A Systematic Review and Thematic Synthesis. **J Diabetes Res**. 2024 Nov 14;2024:3946553. doi: 10.1155/2024/3946553. eCollection 2024.
11. 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. doi: 10.15605/jafes.039.01.14.
12. Mahmoud AA, El-Hawy MA, Allam ET, Salem AH, Abo Hola AS. HbA1c or fructosamine on evaluating glucose intolerance in children with beta-thalassemia. **Pediatr Res**. 2024 Oct;96(5):1292-1298. doi: 10.1038/s41390-024-03146-y.
13. Rodríguez-Segade S, Rodríguez J, Camiña F. Corrected Fructosamine improves both correlation with HbA1C and diagnostic performance. **Clin Biochem**. 2017 Feb;50(3):110-115. doi: 10.1016/j.clinbiochem.2016.10.014.
14. Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. **Blood.** 2008 Nov 15;112(10):4284-91. doi: 10.1182/blood-2008-04-154112.
15. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. **Lancet Diabetes Endocrinol.** 2014 Apr;2(4):279-288. doi: 10.1016/S2213-8587(13)70199-2.

16. Tahara Y, Shima K. Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. **Diabetes Care.** 1995 Apr;18(4):440-7. doi: 10.2337/diacare.18.4.440.
17. Baker JR, O'Connor JP, Metcalf PA, Lawson MR, Johnson RN. Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. **Br Med J (Clin Res Ed)**. 1983 Sep 24;287(6396):863-7. doi: 10.1136/bmj.287.6396.863.
18. 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 Jun 17;62(12):2526-2533. doi: 10.1515/cclm-2024-0591.
19. Doumatey AP, Feron H, Ekoru K, Zhou J, Adeyemo A, Rotimi CN. Serum fructosamine and glycemic status in the presence of the sickle cell mutation. **Diabetes Res Clin Pract**. 2021 Jul;177:108918. doi: 10.1016/j.diabres.2021.108918.
20. 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 Jun 28;78:100240. doi: 10.1016/j.clinsp.2023.100240. eCollection 2023.
21. Malmström H, Walldius G, Grill V, Jungner I, Gudbjörnsdottir S, Hammar N. Fructosamine is a useful indicator of hyperglycaemia and glucose control in clinical and epidemiological studies--cross-sectional and longitudinal experience from the AMORIS cohort. **PLoS One.** 2014 Oct 29;9(10):e111463. doi: 10.1371/journal.pone.0111463. eCollection 2014.