



Glycemic Variability: What Does Hemoglobin A1c Not Reveal About Clinical Risk?

Variabilidade glicêmica: o que a hemoglobina glicada não revela sobre o risco clínico?

Variabilidad glucémica: ¿qué no revela la hemoglobina glucosilada sobre el riesgo clínico?

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ABSTRACT

Introduction: Glycated hemoglobin (HbA1c) is widely used to assess glycemic control; however, it does not fully characterize glucose fluctuations or episodes of hypoglycemia and hyperglycemia. **Objective:** To analyze the scientific evidence on glycemic variability, its relationship with HbA1c, and its implications for clinical risk assessment in patients with diabetes mellitus. **Methods:** An integrative literature review was proposed to synthesize original studies, systematic reviews, meta-analyses, and clinical guidelines addressing glycemic variability and continuous glucose monitoring. **Results:** The reference literature indicates that metrics such as time in range, time below range, time above range, and glycemic coefficient of variation complement HbA1c by characterizing glucose fluctuation patterns and identifying clinically relevant glycemic events. However, the independent prognostic contribution of glycemic variability to long-term outcomes remains uncertain. **Conclusion:** Integrating HbA1c with continuous glucose monitoring metrics may improve the assessment of metabolic control and support individualized treatment. Nevertheless, these indicators should be interpreted in the clinical context and in light of the limitations of the available evidence.

Keywords: Diabetes Mellitus; Glycated Hemoglobin; Continuous Glucose Monitoring; Glycemic Variability.

RESUMO

Introdução: A hemoglobina glicada (HbA1c) é amplamente utilizada para avaliar o controle glicêmico, mas não caracteriza integralmente as oscilações das concentrações de glicose nem a ocorrência de episódios de hipoglicemia e hiperglicemia. **Objetivo:** Analisar as evidências científicas sobre a variabilidade glicêmica, suas relações com a HbA1c e suas implicações para a avaliação do risco clínico em pacientes com diabetes mellitus. **Métodos:** Revisão integrativa da literatura, proposta para reunir estudos originais, revisões sistemáticas, metanálises e diretrizes sobre variabilidade glicêmica e monitorização contínua da glicose. **Resultados:** A literatura de referência indica que indicadores como tempo no intervalo-alvo, tempo abaixo e acima do intervalo-alvo e coeficiente de variação glicêmica complementam a HbA1c, permitindo caracterizar padrões de oscilação e identificar episódios glicêmicos clinicamente relevantes. Entretanto, a contribuição prognóstica independente da variabilidade glicêmica para desfechos de longo prazo permanece incerta. **Conclusão:** A integração da HbA1c com as métricas da monitorização contínua da glicose pode ampliar a avaliação do controle metabólico e favorecer a individualização do tratamento. Contudo, a interpretação desses indicadores deve considerar o contexto clínico e as limitações das evidências disponíveis.

Palavras-chave: Diabetes Mellitus; Hemoglobina A Glicada; Monitorização Contínua da Glicose; Variabilidade da Glicose.



RESUMEN

Introducción: La hemoglobina glucosilada (HbA1c) se utiliza ampliamente para evaluar el control glucémico, pero no caracteriza completamente las fluctuaciones de las concentraciones de glucosa ni la aparición de episodios de hipoglucemia e hiperglucemia. Objetivo: Analizar la evidencia científica sobre la variabilidad glucémica, su relación con la HbA1c y sus implicaciones para la evaluación del riesgo clínico en pacientes con diabetes mellitus. Métodos: Se propuso una revisión integrativa de la literatura para sintetizar estudios originales, revisiones sistemáticas, metanálisis y guías clínicas sobre variabilidad glucémica y monitorización continua de la glucosa. Resultados: La literatura de referencia indica que los indicadores de tiempo en rango, tiempo por debajo del rango, tiempo por encima del rango y coeficiente de variación glucémica complementan la HbA1c, al permitir caracterizar los patrones de fluctuación e identificar episodios glucémicos clínicamente relevantes. Sin embargo, la contribución pronóstica independiente de la variabilidad glucémica a los resultados clínicos a largo plazo sigue siendo incierta. Conclusión: La integración de la HbA1c con las métricas de monitorización continua de la glucosa puede ampliar la evaluación del control metabólico y favorecer la individualización del tratamiento. No obstante, estos indicadores deben interpretarse considerando el contexto clínico y las limitaciones de la evidencia disponible.

Palabras clave: Diabetes Mellitus; Hemoglobina Glucosilada; Monitorización Continua de la Glucosa; Variabilidad Glucémica.

1. INTRODUCTION

Glycated hemoglobin (HbA1c) is widely used in clinical practice for the diagnosis and monitoring of diabetes mellitus because it reflects average glycemic exposure over the preceding two to three months. Its establishment as an indicator of metabolic control has contributed to the definition of therapeutic targets and the assessment of the risk of chronic complications. However, although HbA1c is a fundamental measure, it has important limitations because it does not describe the distribution of glucose concentrations throughout the day, the frequency and duration of hypoglycemic episodes, or the magnitude of glycemic fluctuations.¹

In this context, glycemic variability has received increasing attention as a complementary dimension of metabolic control. This phenomenon encompasses fluctuations in glucose concentrations over time, including variations between different days and intraday oscillations associated with meals, physical activity, stress, and medication effects. Although the independent relationship between glycemic variability and clinical outcomes remains uncertain, particularly regarding the risk of



macrovascular complications, studies suggest that certain characteristics of these fluctuations may help identify patterns of poor metabolic control that are not captured by HbA1c alone.²

The development of continuous glucose monitoring has expanded the possibilities for assessing glycemic profiles by enabling the identification of hyperglycemic and hypoglycemic patterns, quantification of time in range (TIR), estimation of time below and above range, and calculation of variability indicators such as the coefficient of variation. These metrics provide complementary information to HbA1c and may support treatment individualization, particularly in patients receiving insulin therapy, experiencing recurrent hypoglycemic episodes, or presenting discrepancies between laboratory values and clinical manifestations.³

Despite these advances, incorporating glycemic variability indicators into clinical decision-making requires careful interpretation. The availability of multiple metrics does not necessarily mean that all have equivalent prognostic value or that their isolated use leads to better clinical outcomes. Furthermore, conditions that affect erythrocyte turnover, such as anemia, hemoglobinopathies, and chronic kidney disease, may compromise HbA1c interpretation, reinforcing the importance of integrating different sources of information when assessing glycemic control.⁴

Against this background, this article aims to critically review the scientific evidence on glycemic variability and metrics derived from continuous glucose monitoring, discussing their relationships with HbA1c, their potential to identify metabolic risks not captured by average glucose levels, and their applications in clinical practice. It also seeks to analyze the methodological limitations and prognostic implications of these parameters, emphasizing their actual contribution to therapeutic decision-making and individualized care for patients with diabetes mellitus.

2. METHODOLOGY

This study was designed as an integrative literature review with a descriptive and analytical approach, aiming to examine the scientific evidence on glycemic variability, its relationship with glycated hemoglobin (HbA1c), and its contribution to clinical risk assessment in patients with diabetes mellitus.

The literature search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, and Virtual Health Library (VHL) databases. Controlled descriptors and free-text terms in Portuguese, English, and Spanish were combined using the Boolean operators AND and OR. Search terms included



“glycemic variability,” “glucose variability,” “hemoglobin A1c,” “continuous glucose monitoring,” “time in range,” “hypoglycemia,” and “diabetes mellitus,” along with their corresponding terms in the other languages.

Eligible publications included original studies, systematic reviews, meta-analyses, consensus documents, and clinical guidelines addressing glycemic variability, metrics derived from continuous glucose monitoring, and their associations with clinical outcomes, including hypoglycemia, hyperglycemia, microvascular and macrovascular complications, hospitalizations, and mortality. Publications discussing the limitations of HbA1c and the clinical usefulness of complementary glycemic assessment parameters were also considered.

Duplicate studies, publications unrelated to the review objective, isolated case reports, editorials, letters to the editor without relevant data, and studies whose available information did not allow adequate assessment of their contribution to the research question were excluded. Selection initially involved screening titles and abstracts, followed by full-text assessment of potentially eligible publications.

Data extraction included authorship, year of publication, country, study design, population, diabetes type, glycemic indicators assessed, clinical outcomes investigated, and main findings. Particular attention was given to parameters complementary to HbA1c, including time in range (TIR), time below range (TBR), time above range (TAR), and the coefficient of glycemic variation.

The findings were organized into thematic categories concerning the limitations of HbA1c, glycemic variability parameters, associations with clinical outcomes, the applicability of continuous glucose monitoring, and implications for treatment individualization. The evidence was synthesized qualitatively and critically, considering the consistency of findings, characteristics of the populations studied, methodological limitations, and the potential influence of confounding factors on observed associations. No meta-analysis was performed because the approach focused on the critical integration of heterogeneous evidence and its applicability to clinical practice.

3. RESULTS AND DISCUSSION

3.1. Limitations of glycated hemoglobin in the assessment of glycemic control

Glycated hemoglobin (HbA1c) is one of the main indicators used to assess glycemic control and the risk of chronic complications of diabetes mellitus. However, because it estimates average



glycemic exposure over approximately two to three months, this parameter does not directly identify the frequency, duration, or magnitude of glycemic fluctuations, nor does it adequately distinguish episodes of hypoglycemia from those of hyperglycemia.⁵

Patients with similar HbA1c values may exhibit distinct glycemic profiles, with relevant differences in glucose stability and the time spent at extreme glucose levels. This limitation demonstrates that average glycemia, although fundamental, does not fully represent the quality of metabolic control. The international consensus on continuous glucose monitoring emphasizes that sensor-derived data complement HbA1c by identifying fluctuation patterns and glycemic events that are not captured by this measure alone.⁶

In addition to the limitations inherent in representing an average, HbA1c interpretation may be compromised by conditions that alter erythrocyte lifespan or interfere with laboratory measurement, including certain anemias, hemoglobinopathies, blood transfusions, and chronic kidney disease. Under these circumstances, the relationship between HbA1c and actual glycemic exposure may become less reliable, reinforcing the need to integrate laboratory results with clinical data and, when available and indicated, continuous glucose monitoring metrics.⁷

3.2. Glycemic variability and the characterization of metabolic fluctuations

Glycemic variability encompasses fluctuations in glucose concentrations over time and can be characterized using indicators such as standard deviation, coefficient of variation, and mean amplitude of glycemic excursions. These parameters describe different aspects of glucose behavior and contribute to a more comprehensive assessment of metabolic control.⁸

Among the available indicators, the coefficient of variation is calculated by dividing the standard deviation by mean glucose and multiplying the result by 100. By expressing the relative dispersion of glucose values, it allows comparisons between profiles with different mean glucose levels. The international consensus recommends its use as the primary measure of variability derived from continuous glucose monitoring, considering values of 36% or lower a reference for glycemic stability in most clinical situations covered by the recommendations.⁹

However, the coefficient of variation should not be interpreted in isolation. Although greater dispersion of glucose values may indicate increased metabolic instability, this indicator does not directly quantify the time a patient spends in hypoglycemia or hyperglycemia. Therefore, combining it



with time-based metrics for different glucose ranges helps identify not only the magnitude of fluctuations but also their distribution and clinical relevance.¹⁰

Glycemic variability has also been investigated in relation to oxidative stress, endothelial dysfunction, and mechanisms involved in diabetes-associated vascular injury. Despite the pathophysiological plausibility of these relationships, evidence that variability constitutes an independent risk factor for cardiovascular events remains limited by study heterogeneity and the influence of factors such as disease duration, comorbidities, and treatment. Thus, observational associations should be interpreted cautiously, without assuming that reducing variability alone necessarily leads to better clinical outcomes.¹¹

3.3. Time in range and continuous glucose monitoring metrics

Continuous glucose monitoring makes it possible to assess the temporal distribution of glucose concentrations and identify periods of exposure to hypoglycemia, the target range, and hyperglycemia. The most widely used metrics include time in range (TIR), time below range (TBR), and time above range (TAR).¹²

Standardized representations facilitate the identification of abnormalities that may be overlooked when analyzing HbA1c or isolated capillary glucose measurements. Furthermore, the simultaneous visualization of these indicators makes it possible to relate observed patterns to meal times, sleep periods, physical activity, and medication administration, supporting individualized interventions.¹³

TIR is particularly relevant because it expresses the proportion of the monitoring period during which glucose remains within the defined target range. Its interpretation alongside TBR and TAR helps distinguish situations in which the primary problem is exposure to hyperglycemia from those in which therapeutic safety is compromised by hypoglycemic episodes. This distinction is important because reducing HbA1c should not be pursued without considering the risk of adverse events.¹⁴

3.4. Glycemic variability and implications for clinical risk

Clinical risk assessment in people with diabetes requires consideration of average glycemic exposure, the frequency of extreme events, and the stability of metabolic control. In this context, glycemic variability and metrics derived from continuous glucose monitoring may provide relevant



additional information, particularly when HbA1c is inconsistent with the clinical presentation or when unrecognized hypoglycemic episodes are suspected.¹⁵

Identifying prolonged periods of glucose below the target range is particularly important in older adults, individuals with chronic kidney disease, and patients treated with insulin or medications associated with hypoglycemia. In these groups, an increased TBR may indicate the need to reassess the treatment regimen, considering the possibility of excessive doses, irregular food intake, or other predisposing factors.¹⁶

Regarding chronic complications, observational studies and analyses of glycemic data have reported associations between TIR and indicators of diabetes-related complications. However, the strength of the evidence varies according to the outcome investigated, and the existence of an association does not, by itself, establish causality. The international consensus recognizes the clinical usefulness of continuous glucose monitoring metrics while also highlighting limitations in the available evidence for establishing definitive independent prognostic relationships across all long-term outcomes.¹⁷

Consequently, glycemic variability should be understood as a complementary dimension of metabolic assessment rather than a substitute for HbA1c or other clinical factors used in risk stratification. Integrated analysis may improve the identification of relevant patterns, but interpretation must account for diabetes duration, comorbidities, treatment, data quality, and individual patient characteristics.

3.5. Integration of glycemic metrics into clinical decision-making

Incorporating continuous glucose monitoring metrics into clinical practice makes it possible to tailor interventions according to the predominant pattern of glycemic abnormality. In patients with reduced TIR and elevated TAR without substantial hypoglycemic exposure, assessment may prioritize strategies to improve hyperglycemia. Conversely, when TBR is elevated, therapeutic safety should receive priority, with investigation of factors associated with low glucose episodes.¹⁸

Another relevant parameter is the glucose management indicator (GMI), calculated from mean glucose obtained through continuous glucose monitoring. Although it may assist data interpretation, GMI is not equivalent to laboratory-measured HbA1c. Differences between these parameters may reflect variations in glycemic exposure during the periods assessed or conditions that interfere with



HbA1c interpretation. Therefore, relevant discrepancies should be investigated rather than automatically interpreted as an error in either measurement.¹⁹

The use of these metrics also presents practical limitations related to sensor availability, cost, data quality, and healthcare professionals' experience in interpreting reports. In addition, standardized targets should not be applied indiscriminately to all patients, particularly those with clinical frailty, increased hypoglycemia risk, or specific therapeutic needs. Thus, the main contribution of continuous glucose monitoring is to complement conventional assessment and enable a more detailed analysis of glucose behavior. Integrating HbA1c with TIR, TBR, TAR, and the coefficient of variation may support individualized therapeutic decisions, provided that these metrics are interpreted within the clinical context and in light of the limitations of the available evidence.²⁰

In summary, glycemic variability represents an important dimension of metabolic control that is not fully captured by HbA1c. Metrics derived from continuous glucose monitoring characterize glucose fluctuations, identify episodes of hypoglycemia and hyperglycemia, and reveal opportunities for treatment individualization. However, the independent prognostic contribution of these indicators and the specific impact of reducing variability on long-term clinical outcomes require further investigation.

5. FINAL CONSIDERATIONS

Glycemic variability represents a relevant dimension of metabolic control assessment in patients with diabetes mellitus, complementing the information provided by glycated hemoglobin. Although HbA1c remains a fundamental indicator, its isolated use does not adequately identify glycemic fluctuations, the frequency of hypoglycemic and hyperglycemic episodes, or the time spent at glucose concentrations outside the target range.

Continuous glucose monitoring expands clinical assessment by providing indicators such as time in range, time below and above range, and the coefficient of glycemic variation. Integrated interpretation of these metrics may help identify patterns of poor metabolic control, recognize situations associated with increased hypoglycemia risk, and guide the individualization of therapeutic strategies.

However, the relationship between glycemic variability and clinical outcomes must be interpreted in light of methodological limitations and the heterogeneity of the available evidence.



Although pathophysiological mechanisms and observational associations support the relevance of this parameter, further studies are needed to clarify its independent prognostic contribution and the effects of reducing variability on cardiovascular complications and other long-term outcomes.

In conclusion, contemporary diabetes mellitus assessment should integrate HbA1c, continuous glucose monitoring metrics, and individual clinical characteristics. This approach provides a more comprehensive understanding of glycemic profiles and supports therapeutic decisions guided not only by reductions in average glucose levels but also by metabolic safety and the prevention of adverse glycemic events.



REFERENCES

1. Karczewski D, Karczewski T, Olsen M. Glycated hemoglobin and prediabetes: a systematic review of HbA1c thresholds for type 2 diabetes prevention. **J Clin Med.** 2026;15(12):4690. doi:10.3390/jcm15124690.
2. Andreadi A, Andreadi S, Todaro F, Cerilli M, Lodeserto P, Pinto G, *et al.* Glycemic variability and continuous glucose monitoring in occupational health: a narrative review of emerging evidence and potential applications in working populations. **Healthcare (Basel).** 2026;14(13):1979. doi:10.3390/healthcare14131979.
3. Williams E Jr, Rand C, Ayers A, Ho C, Dunova A, Klonoff D, *et al.* The evolving landscape of continuous glucose monitoring metrics in type 1 diabetes: narrative literature review. **JMIR Diabetes.** 2026;11:e92455. doi:10.2196/92455.
4. Fehér MD, Ilea CDN, Vesa CM, Venter AC, Birsan SD, Ghitea TC, *et al.* Glycemic status and glycemic variability related to mortality and morbidity in critically ill diabetic and non-diabetic patients: a prospective observational study. **Clin Pract.** 2026;16(8):145. doi:10.3390/clinpract16080145.
5. Yapanis M, James S, Craig ME, O'Neal D, Ekinici EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. **J Clin Endocrinol Metab.** 2022;107(6):e2221-e2236. doi:10.1210/clinem/dgac034.
6. Lazar S, Ionita I, Reurean-Pintilei D, Timar R, Luca SA, Timar B. To what extent is HbA1c associated with glycemic variability in patients with type 1 diabetes? A retrospective, noninterventional study. **J Clin Med.** 2024;13(2):450. doi:10.3390/jcm13020450.
7. Bhargava S, Mahato K, Manocha A, Kankra M, Singla P, Sharma A, *et al.* Interpreting HbA1c in presence of deficiency anemias. **Indian J Clin Biochem.** 2021;36(3):360-4. doi:10.1007/s12291-020-00896-4.
8. Agmon O, Sigawi T, Ilan Y. The constrained disorder principle: a novel framework for understanding glycemic variability and optimizing diabetes management. **Endocr Metab Sci.** 2025; [volume and article number to confirm]. doi:10.1016/j.endmts.2025.100262.
9. Fatulla P, Imberg H, Sterner Isaksson S, Hirsch IB, Mårtensson J, Liljebäck H, *et al.* Evaluating the adequacy of coefficient of variation and standard deviation as metrics of glucose variability in type 1 diabetes based on data from the GOLD and SILVER trials. **Diabetes Technol Ther.** 2025;27(8):606-12. doi:10.1089/dia.2024.0540.
10. Urakami T, Terada H, Tanabe S, Mine Y, Aoki M, Aoki R, *et al.* Clinical significance of coefficient of variation in continuous glucose monitoring for glycemic management in children and adolescents with type 1 diabetes. **J Diabetes Investig.** 2024;15(11):1669-74. doi:10.1111/jdi.14303.



11. Ohara M, Takahashi N, Takehana N, Osaka N, Sugita H, Terasaki M, *et al.* Association of glycemic variability with oxidative stress and AGE accumulation in type 2 diabetes. **Sci Rep.** 2025;16(1):2055. doi:10.1038/s41598-025-31845-x.
12. Yoo JH, Kim JH. Time in range from continuous glucose monitoring: a novel metric for glycemic control. **Diabetes Metab J.** 2020;44(6):828-39. doi:10.4093/dmj.2020.0257.
13. Pi L, Zheng Y, Shi X, Wang Z, Zhou Z. Using point-of-care HbA1c to facilitate the identification of diabetes and abnormal glucose regulation in primary healthcare settings. **Front Public Health.** 2023;11:1078361. doi:10.3389/fpubh.2023.1078361.
14. Guo QY, Lu B, Guo ZH, Feng ZQ, Yuan YY, Jin XG, *et al.* Continuous glucose monitoring defined time-in-range is associated with sudomotor dysfunction in type 2 diabetes. **World J Diabetes.** 2020;11(11):489-500. doi:10.4239/wjdv11.i11.489.
15. Al Hayek A, Al Mashali M, Al Dawish MA. Evaluation of glycemia risk index and continuous glucose monitoring-derived metrics in type 1 diabetes: a real-world observational study. **J Diabetes Metab Disord.** 2025;24(1):59. doi:10.1007/s40200-025-01569-w.
16. Canha D, Choudhary P, Cosson E, Banu I, Barraud S, Valéro R, *et al.* Time below range alone is insufficient to identify severe hypoglycaemia risk in type 1 diabetes: the critical role of hypoglycaemia awareness: results from the SFDT1 study. **Diabetologia.** 2025;68(12):2719-31. doi:10.1007/s00125-025-06536-x.
17. De Meulemeester J, Charleer S, Visser MM, De Block C, Mathieu C, Gillard P. The association of chronic complications with time in tight range and time in range in people with type 1 diabetes: a retrospective cross-sectional real-world study. **Diabetologia.** 2024;67(8):1527-35. doi:10.1007/s00125-024-06171-y.
18. Miller EM. Using continuous glucose monitoring in clinical practice. **Clin Diabetes.** 2020;38(5):429-38. doi:10.2337/cd20-0043.
19. Sager-La Ganga C, Arranz-Martin JA, Jiménez-Díaz J, Hernando-Alday I, Navas-Moreno V, Fandiño García MDM, *et al.* The GMI/HbA1c ratio does not independently predict diabetic retinopathy in adults with type 1 diabetes. **Sci Rep.** 2025;15(1):35825. doi:10.1038/s41598-025-19705-0.
20. Bernardi FA, Alves D, Crepaldi N, Yamada DB, Lima VC, Rijo R. Data quality in health research: integrative literature review. **J Med Internet Res.** 2023;25:e41446. doi:10.2196/41446.