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ORIGINAL RESEARCH

Glycemic variability: adverse clinical outcomes and how to improve it? - A review of the evidence

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed publication is a narrative review examining glycemic variability, i.e., the magnitude and frequency of blood glucose fluctuations, both throughout the day and between different visits. The authors describe observational and experimental studies in which greater glycemic instability has been associated with hypoglycemia, microvascular and macrovascular complications, mortality, and other adverse outcomes. The review also discusses the contribution of continuous glucose monitoring, medications, diet, and exercise to reducing these fluctuations.In section 3.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study contributes to two specific points: the hypothesis that rapid fluctuations may promote oxidative stress and the fact that glycemic variability can help identify a higher risk of severe hypoglycemia beyond glycated hemoglobin alone. Independent evidence directly confirms the association between greater variability and an increased risk of hypoglycemia in type 1 diabetes; a human study also finds a correlation between acute fluctuations and a urinary marker of oxidative stress. However, these data do not prove that variability alone causes all diabetic complications. An analysis of the Diabetes Control and Complications Trial did not observe an independent contribution of intraday variability to microvascular complications after adjustment for mean glycemia. Overall, the narrative is moderately supported, especially regarding the assessment of hypoglycemic risk.

ONLINE ARTICLE

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether glycemic variability, in addition to mean glycemia and glycated hemoglobin or HbAIc (an index of the average glycemia over the last two to three months), is linked to unfavorable clinical outcomes and which tools can reduce it. The underlying hypothesis is that it is not only important how high the glycemia is on average, but also how frequently and how rapidly it increases or decreases.The relevance to paragraph 3.1 is precise. The publication was used to support the claim that marked fluctuations can be biologically relevant and that variability indices help estimate the risk of hypoglycemia, often in a complementary way to HbAIc. Being a narrative review, the analyzed study synthesizes results from previous research but does not produce a new experimental comparison or a new patient cohort. It can therefore describe the convergence of the available literature, but cannot by itself demonstrate a causal relationship between glycemic variability and individual complications.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the literature, not a clinical study with participants enrolled directly by the authors. The text distinguishes between short-term variability, observable within a single day or between consecutive days, and long-term variability, calculated through repeated measurements of fasting glycemia, post-meal glycemia, or HbAIc.Several indicators are described. The standard deviation indicates how much values deviate from their mean. The coefficient of variation relates this dispersion to the mean glycemia. MAGE quantifies the amplitude of major excursions between peaks and nadirs. Continuous glucose monitoring, or CGM, detects frequent values in the interstitial fluid and allows for a more detailed observation of the daily profile compared to point-in-time measurements.The available material does not report a reproducible bibliographic search strategy, the databases consulted, formal inclusion or exclusion criteria for the studies, a standardized risk-of-bias assessment, or a quantitative meta-analysis. Consequently, it is not possible to establish with precision how all the discussed studies were selected, nor to formally estimate the heterogeneity of the results.

4. RESULTS

The review reports that greater glycemic variability has been associated, in various studies, with a higher frequency of hypoglycemia, less favorable cardiovascular and microvascular outcomes, and increased mortality. The authors emphasize that HbAIc represents an average value and may not show the fluctuations between glycemic peaks and rapid drops in glycemia.Regarding the relevant passage in the book, the central finding is that indices such as standard deviation, coefficient of variation, MAGE, and glycemic risk indices have been repeatedly associated with a higher probability of hypoglycemia. The review also highlights that CGM allows for the recognition of nocturnal and post-meal oscillations, phenomena that isolated measurements may fail to detect.The text also examines the possible biological link between rapid glucose oscillations and oxidative stress, which is an imbalance where the production of oxidizing molecules exceeds the body's defenses. However, the publication does not provide a single overall quantitative estimate of the effect, because it collects studies with different populations, metrics, and observation periods. It does not report its own sample size, follow-up, or original statistical values, as it is neither an intervention study nor a meta-analysis.

5. INTERPRETATION

In simple terms, two people can have the same HbAIc but very different daily patterns: relatively stable glycemia or frequent ups and downs. The publication analyzed argues that this second piece of information can be clinically useful, especially when it is necessary to identify those most at risk for episodes of excessively low blood sugar.The segment of the scientific chain effectively documented by the review is: wider glycemic oscillations greater exposure to extreme values and greater association with hypoglycemia; in parallel, acute oscillations association with markers of oxidative stress. The review proposes that oxidative stress, inflammation, and vascular alterations may contribute to complications, but this sequence has not been demonstrated in a causal and uniform manner in humans.The most solid point, therefore, is not the claim that reducing variability necessarily prevents all

diabetic complications. It is rather the recognition that glycemic stability adds information beyond the average alone and that high variability can signal a greater risk of hypoglycemia. The strength of the interpretation changes based on the context: type of diabetes, insulin therapy, indicator used, and quality of the measurement.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the passage regarding hypoglycemia comes from a new analysis of data from the Diabetes Control and Complications Trial. In this cohort of people with type 1 diabetes, Kilpatrick and colleagues evaluated whether mean glycemia and intraday glycemic variability added information to HbA1c in predicting episodes of severe hypoglycemia. After adjusting for HbA1c, each 1 mmol/L increase in the glycemic standard deviation was associated with a 1.09-fold increase in the risk of a first severe episode; for the fifth episode, the ratio rose to 1.12. This is a prognostic association, not proof that variability causes hypoglycemia, but it confirms that HbA1c alone does not exhaust the risk assessment [1].For the mechanistic passage, Monnier and colleagues compared 21 people with type 2 diabetes and 21 controls matched for age and sex. In participants with diabetes, a greater amplitude of glycemic excursions, measured with MAGE via CGM, was associated with higher urinary excretion of 8-iso-prostaglandin F2a, an indicator of oxidative stress. The correlation between MAGE and this marker was positive and strong, with r=0.86 and P<0.001. The study confirms the biological consistency of the narrative, but the case-control design and the small sample size do not allow for proof that oscillations are the cause of vascular complications [2].The two studies are independent of the publication analyzed and support different parts of the same narrative: the first concerns the clinical prediction of severe hypoglycemia, the second a possible biological mechanism of glycemic oscillations. Together, they reinforce the idea that monitoring glycemic stability can complement, without replacing, mean glycemia and HbA1c.

7. CONFLICTING EVIDENCE

Significant conflicting evidence concerns the relationship between glycemic variability and microvascular complications. In the Diabetes Control and Complications Trial, Lachin and colleagues analyzed intraday and inter-visit glycemic variations in people with type 1 diabetes. After adjusting for mean glycemia, no measure of intraday variability was found to be associated with the development or progression of retinopathy, nephropathy, or cardiovascular autonomic neuropathy. The authors therefore concluded that the available glycemic profiles did not provide strong and consistent evidence of an independent effect of variability on microvascular complications [3].This result does not contradict the association between variability and the risk of hypoglycemia, as the outcomes are different. However, it reduces the certainty of the broader idea that high oscillations directly cause all diabetes complications. Furthermore, the study used seven-point quarterly glycemic profiles rather than modern CGM: while this may limit the ability to detect short excursions, it does not justify ignoring the negative result.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication reviewed from the independent research used to confirm or define the book's narrative progression.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on diabetes, CGM, and glycemic variability	Synthesizes associations between high variability, hypoglycemia, complications, and mortality; discusses potential reduction strategies.	biologically consistent evidence	moderate
[1]	Observational, new cohort analysis	People with type 1 diabetes from the Diabetes Control and Complications Trial	Higher glycemic standard deviation associated with increased risk of repeated episodes of severe hypoglycemia, even after adjustment for HbA1c.	direct confirmation	moderate
[2]	Case-control	21 people with type 2 diabetes and 21 controls	Higher MAGE associated with greater urinary excretion of an oxidative stress marker.	indirect confirmation	preliminary
[3]	Observational, longitudinal analysis	People with type 1 diabetes from the Diabetes Control and Complications Trial	After adjustment for mean glycemia, intraday variability was not associated with the microvascular complications analyzed.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the idea that average glycemia does not fully describe metabolic control. The best-supported part of the narrative concerns the relationship between greater glycemic variability and a higher risk of severe hypoglycemia, particularly in people treated with insulin. The link between acute fluctuations and oxidative stress is supported at an observational and mechanistic level, but requires validation in larger studies. Conversely, it has not been uniformly demonstrated that reducing variability, independently of average glycemia, prevents all microvascular or cardiovascular complications.

Aggiornato al 17/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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