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ORIGINAL RESEARCH

Glycemic variability: how do we measure it and why is it important? - Evidence review

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1. ABSTRACT

The analyzed publication is a narrative review dedicated to glycemic variability, i.e., blood glucose fluctuations throughout the day and between different days. Its objective was to explain how these fluctuations can be measured, why glycated hemoglobin (HbA1c, an indicator of average blood glucose over the previous months) does not fully describe them, and what their clinical significance might be. The authors primarily discuss the relationship between glycemic spikes, hypoglycemia, oxidative stress, and diabetes complications.In section 3.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that unstable glycemia can have its own biological effects and can help identify the risk of hypoglycemia beyond HbA1c alone. Independent studies confirm that wider acute oscillations are associated with higher markers of oxidative stress and that greater variability is associated with more severe hypoglycemic episodes. Associations with vascular complications and mortality are supported primarily by observational studies; they do not, on their own, prove that reducing variability prevents cardiovascular events.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 has additional clinical significance compared to mean glycemia and HbA1c. The hypothesis discussed by the authors is that rapid fluctuations between high and low glucose levels may contribute to the risk of hypoglycemia and vascular damage, even when mean glycemia appears similar.The relevance to section 3.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns two segments of the narrative: the hypothesis that oscillations promote oxidative stress and vascular alterations, and the observation that variability may estimate the risk of hypoglycemia better than HbA1c alone. The publication subject to the Evidence Review is a narrative review, not a new experimental or clinical study. It can therefore integrate and interpret previously published results, but it cannot directly demonstrate a causal relationship nor establish an effective treatment to reduce complications.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

This work is a narrative review of the literature on glycemic variability in type 1 and type 2 diabetes. The authors describe metrics derived from continuous glucose monitoring, or CGM (a system that repeatedly records glucose levels over twenty-four hours), including standard deviation, coefficient of variation, and MAGE, which stands for mean amplitude of glycemic excursions.The publication summarizes cellular, animal, observational, and clinical studies regarding oxidative stress, hypoglycemia, and microvascular and cardiovascular complications. It does not report a systematic literature search strategy, the databases consulted, the keywords used, the search period, formal inclusion or exclusion criteria, a standardized risk of bias assessment, or a meta-analysis. Since it does not present a new cohort or original intervention, the sample size, follow-up, control group, and endpoints of the original study are not applicable.

4. RESULTS

The central finding of the review is conceptual: two people with similar average glycemia can have very different profiles. One may maintain relatively stable values; the other may alternate between post-meal spikes and rapid drops, including hypoglycemia. HbA1c primarily describes average glucose exposure over time and does not necessarily identify these differences.The authors report that available experiments suggested a more unfavorable biological effect from intermittent exposure to high glucose compared to high but constant exposure. The proposed mechanism involves oxidative stress—an excess of reactive oxygen molecules that can damage cells and blood vessels—and endothelial dysfunction, which is a reduced ability of the inner lining of blood vessels to properly regulate blood flow.The review also highlights that greater glycemic variability is more frequently associated with hypoglycemia. This is particularly relevant for people treated with insulin or drugs that increase insulin secretion. The authors report that variability may explain a greater portion of the future risk of hypoglycemia compared to HbA1c, but they acknowledge that variability indices were not measured using a single, universally accepted method at the time.Regarding microvascular complications, such as retinopathy, nephropathy, and neuropathy, the summarized evidence supports an association with greater variability. However, for major cardiovascular events and mortality, the same review considers the evidence less conclusive. This finding is important: the authors do not present the reduction of variability as a strategy already proven to prevent heart attack, stroke, or death.

5. INTERPRETATION

In simple terms, a highly irregular glycemic curve can expose the body to repeated shifts between excess and deficiency of glucose. This instability can make it more difficult to prevent hypoglycemia and, according to the biological hypothesis discussed, may promote damage signals in the vessels. The segment of the chain documented by the publication subject to the Evidence Review is therefore: wide glycemic oscillations oxidative stress and increased probability of hypoglycemia.The technical detail requires caution. Oxidative stress, inflammation, platelet activation, and

endothelial dysfunction are plausible and biologically consistent mechanisms, but they do not equate to proof that variability causes every complication of diabetes. Furthermore, the significance of a measurement depends on the context: standard deviation and the coefficient of variation measure different aspects, while MAGE favors the widest excursions. Average glycemia can also influence many indices.The book's narrative is therefore supported at the mechanistic and prognostic level: glycemic stability adds information beyond the average alone and can be useful for identifying the risk of hypoglycemia. However, it remains necessary to distinguish between a risk indicator and a proven cause of cardiovascular complications.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the biological link between fluctuations and oxidative stress comes from a case-control study conducted on 21 people with type 2 diabetes and 21 controls matched for age and sex. In participants with diabetes, higher MAGE measured via CGM was strongly associated with greater urinary excretion of 8-iso-prostaglandin F2a, a marker of oxidative stress. The association with MAGE remained significant even after adjusting for other glycemic indicators. This study supports the narrative that wider fluctuations may be accompanied by greater oxidative stress; however, the observational design and small sample size do not allow us to establish that fluctuations are the exclusive cause of vascular damage [1].Regarding the second point in the book, namely the relationship between glycemic instability and severe hypoglycemia, a large population study examined 32,117 children, adolescents, and young adults with type 1 diabetes. Variability measured as a coefficient of variation equal to or greater than 36% was associated with a higher rate of severe hypoglycemia compared to a coefficient of less than 36%: incidence rate ratio 1.52, with a 95% confidence interval from 1.06 to 2.17. Continuous monitoring was also associated with a lower rate of severe hypoglycemia compared to intermittent capillary monitoring. This is an observational association, not proof that the sensor or lower variability alone cause the reduction in events, but it confirms that variability adds relevant clinical information [2].A systematic review with meta-analysis of 75 cohort studies and 2,051,701 participants extended the picture to oscillations observed between successive visits, assessed through HbA1c or fasting glycemia. Comparing the highest quartiles of HbA1c variability with the lowest, the relative risk of all-cause mortality was higher, at 1.63 using the coefficient of variation. The relative risks of cardiovascular disease, kidney disease, and peripheral neuropathy were also higher. These data confirm a prognostic relationship between glycemic instability and worse outcomes, but they primarily concern long-term variations, not the daily excursions recorded by CGM, and remain subject to the confounding typical of observational studies [3].

7. CONFLICTING EVIDENCE

The main caution concerns the transition from association to clinical prevention. In the randomized HEART2D trial, 1,115 people with type 2 diabetes enrolled after a myocardial infarction were assigned to an insulin strategy targeting primarily postprandial glycemia or a strategy targeting primarily basal glycemia. The postprandial strategy achieved lower glycemic excursions after meals, but did not reduce the risk of the first combined cardiovascular event compared to the basal strategy: hazard ratio 0.98, 95% confidence interval from 0.80 to 1.21.This result does not disprove the fact that fluctuations are associated with oxidative stress or hypoglycemia. However, it shows that reducing one component related to variability, postprandial glycemia, did not demonstrate a reduction in cardiovascular events in that context. Furthermore, postprandial glycemia and glycemic variability are not the same thing, and the difference between the strategies achieved in the study may not have been sufficient to modify cardiovascular outcomes [4].

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from independent research selected to confirm or define the specific passages of the book chapter.

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	Variability adds information to mean glycemia and is linked to hypoglycemia, oxidative stress, and potential complications.	biologically consistent evidence	moderate
[1]	Case-control	21 people with type 2 diabetes and 21 controls	Higher MAGE associated with greater urinary excretion of 8-iso-prostaglandin F2a, a marker of oxidative stress.	direct confirmation	moderate
[2]	Population-based observational	32,117 young people with type 1 diabetes	Coefficient of variation ≥36% associated with higher rate of severe hypoglycemia; CGM associated with lower rates of severe hypoglycemia.	direct confirmation	moderate
[3]	Systematic review and meta-analysis of cohorts	75 studies; 2,051,701 participants with diabetes	Greater HbA1c or fasting glycemia variability associated with mortality and certain vascular and microvascular outcomes.	indirect confirmation	moderate
[4]	RCT	1,115 people with type 2 diabetes after myocardial infarction	Reduced postprandial excursions without reduction in combined cardiovascular risk.	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. Glycemic variability is well-supported as a complementary indicator for identifying fluctuations, spikes, rapid drops, and the risk of hypoglycemia. The link with oxidative stress is confirmed at a biological level in humans, but requires larger studies. Associations with vascular complications are moderately supported by cohorts and meta-analysis, without proving that variability is an independent cause. Reducing fluctuations remains a promising goal for monitoring and individualized management, but the direct cardiovascular benefit requires further clinical validation.

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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