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ORIGINAL RESEARCH

Relationship of glucose variability with glycated hemoglobin and mean daily glycemia: post hoc analysis of data from 5 phase 3 studies - Evidence review

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The original study pooled data from five phase III clinical trials to verify whether glycemic variability, i.e., the magnitude of glucose fluctuations throughout the day or between different days, was linked to the main indicators of metabolic control: glycated hemoglobin and mean daily glycemia. The post hoc analysis found that lower intra-day variability was associated with better values for both indicators in the type 1 and type 2 diabetes groups examined.In the section dedicated to postprandial glycemic variability, "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi uses this research to argue that attenuating glycemic fluctuations is accompanied by better metabolic control and fewer episodes of hypoglycemia. The first part is directly consistent with the study; the link to a lower risk of hypoglycemia, however, requires external evidence. Meta-analysis and randomized studies with continuous monitoring show that interventions capable of reducing variability, hyperglycemia, and time spent at low values can simultaneously improve these parameters. However, they do not prove that every single reduced postprandial excursion alone produces such effects, nor that the relationship is identical in all people with diabetes.

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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 glucose fluctuations were linked to the two most common indicators of overall glycemic control: glycated hemoglobin, which roughly reflects average glucose exposure over the previous months, and mean daily glycemia. The hypothesis was that greater glycemic variability could contribute to less favorable values for these parameters.The relevance to the book's section therefore concerns a specific segment of the narrative: blood glucose excursions within the same day, including those following meals, may be associated with less stable metabolic control. The publication did not separately measure postprandial variability as a sole causal factor and did not verify whether reducing it through a specific treatment directly reduces hypoglycemia. It can document statistical associations between measures of variability and glycemic control, not an autonomous causal relationship between each post-meal spike and clinical outcomes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

This is a post-hoc analysis, meaning it was conducted subsequently on data already collected from five phase III clinical trials. The data were grouped into three sets: people with type 2 diabetes treated only with basal insulin, people with type 2 diabetes treated with a basal-bolus regimen (i.e., basal insulin plus mealtime doses), and people with type 1 diabetes.The authors evaluated variability within the day and between different days. Fluctuations were calculated primarily using standard deviation, a measure of the dispersion of values relative to their mean, and the coefficient of variation, a measure that relates dispersion to the mean value. The variability of fasting glycemia, the rate of hypoglycemia, and certain baseline characteristics of the participants were also considered.To estimate the relative weight of the different variables on the outcomes, a generalized boosted model was used—a statistical procedure that combines many decision trees to identify which factors contribute most to predicting a result. The overall sample size, detailed inclusion and exclusion criteria, duration of individual studies, specific treatments, baseline values, and numerical estimates of the model are not reported in the available material, which consists only of the abstract.

4. RESULTS

The central finding is that intra-day variability, calculated using standard deviation, had a statistically significant influence on both glycated hemoglobin and mean daily glycemia in all three groups analyzed. In simple terms, people with more fluctuating blood glucose levels throughout the day tended to have less favorable average indicators of glycemic control.In the group with type 2 diabetes treated with basal insulin alone, the day-to-day variability of fasting glycemia, intra-day variability calculated using the coefficient of variation, and the rate of hypoglycemia also significantly influenced glycated hemoglobin. The abstract does not report the detailed direction of the effects for each variable, nor does it provide coefficients, confidence intervals, P-values, sample sizes, or percentages of explained variance. It is therefore not possible to quantify how much each factor weighed compared to the others.The authors concluded that lower intra-day variability was associated with an improvement in mean daily glycemia and glycated hemoglobin. This supports the section of the book regarding better metabolic control. However, the abstract does not report that reducing variability directly reduced the risk of hypoglycemia; rather, it reports that the rate of hypoglycemia contributed to the prediction of glycated hemoglobin in a specific subgroup.

5. INTERPRETATION

An average glucose value may appear acceptable even when it masks frequent fluctuations between high and low levels. For this reason, glycemic variability provides information distinct from glycated hemoglobin: it describes how stable glucose levels are throughout the day. The publication analyzed shows that these oscillations are closely linked to both the daily average glucose and glycated hemoglobin.The chain of events documented by the research is: greater intra-day variability less favorable average glycemic control. The reference to postprandial excursions is plausible because meals can contribute significantly to daily oscillations, but the study did not isolate post-meal spikes, nor did it demonstrate that they are the predominant component in every person or therapy.The additional passage in the book, which

suggests that stabilizing excursions is associated with fewer hypoglycemic events, is biologically consistent but is not directly proven by this analysis. To verify this, studies are needed that measure both variability and time spent below the hypoglycemic threshold in the same comparison, preferably with random assignment to different therapeutic strategies.

6. INDEPENDENT SUPPORTING EVIDENCE

A meta-analysis of 15 randomized studies, totaling 2,461 participants with type 1 or type 2 diabetes, compared continuous glucose monitoring with standard care. Compared to the control, continuous monitoring was associated with an average reduction in glycated hemoglobin of 0.17 percentage points, 70.74 more minutes per day in the target glycemic range, and reductions in variability, time above range, and time below range. This evidence confirms the coexistence of improved average control, fewer fluctuations, and less exposure to hypoglycemia, but it does not separate the effect of variability alone from that of the entire sensor-based intervention. Heterogeneity between studies was high and follow-up was short, ranging from 12 to 36 weeks [1].The GOLD-3 study, a randomized crossover trial conducted in people with type 1 diabetes on multiple daily insulin injections, offers confirmation closer to the book's formulation. During the use of continuous monitoring, the coefficient of glycemic variation fell from 0.40 to 0.37 compared to conventional therapy, with a difference of –0.03; standard deviation and mean amplitude of glycemic excursions also decreased. In the same comparison, the daily time below 70 mg/dL decreased from 4.79% to 2.79%, while the relative risk of time spent below that threshold was 0.58. This indicates a 42% reduction in time in hypoglycemia during the intervention. The result is experimental and consistent with greater glycemic stability, but continuous monitoring also changes therapeutic decisions; therefore, it does not prove that lower variability, in isolation, is the cause of the effect [2].

7. CONFLICTING EVIDENCE

Evidence does not indicate that improvements in every glycemic measure always occur in tandem. In a six-month randomized study of 224 people with type 2 diabetes on intensive insulin therapy, flash monitoring reduced time in hypoglycemia below 70 mg/dL by 0.47 hours per day, equal to 43%, and below 55 mg/dL by 0.22 hours per day, equal to 53%. However, the change in glycated hemoglobin did not differ between the sensor group and the control group: –0.29% versus –0.31%, with P=0.8222. This data shows that less time in hypoglycemia can occur even without an average benefit in glycated hemoglobin across the entire study population [3].A small observational study of 108 people with type 2 diabetes also found that the group with glycated hemoglobin below 7% had lower glycemic variability compared to the group with values of at least 7%, but still tended to experience silent hypoglycemia more frequently and for longer durations; the differences in hypoglycemia were not statistically significant. This observation does not contradict the potential utility of reducing fluctuations, but it signals that low glycated hemoglobin and lower variability alone do not guarantee the absence of hypoglycemia [4].These findings define the main interpretive limitation: average control, variability, and hypoglycemia are linked, but they are not synonymous. Their relationship depends on the type of diabetes, insulin treatment, monitoring technology, therapeutic behaviors, and the measure of variability used.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from independent research that confirms or defines the narrative arc of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Post hoc analysis of five phase III studies	Type 1 and type 2 diabetes, in three therapeutic groups	Lower intra-day variability associated with more favorable glycated hemoglobin and mean daily glycemia	direct confirmation	moderate
[1]	Systematic review and meta-analysis of RCTs	2,461 people with type 1 or type 2 diabetes	Reduction in glycated hemoglobin, variability, and time below range with continuous monitoring	direct confirmation	moderate
[2]	Crossover RCT	Adults with type 1 diabetes on multi-injection therapy	Reduction in variability and time in hypoglycemia during continuous monitoring	direct confirmation	moderate
[3]	Multicenter open-label RCT	224 adults with type 2 diabetes on intensive insulin therapy	Reduction in hypoglycemia without overall difference in glycated hemoglobin change	discordant evidence	moderate
[4]	Cross-sectional observational study	108 people with type 2 diabetes monitored for 72 hours	Lower variability in the group with lower glycated hemoglobin, but a tendency toward more silent hypoglycemia	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the association between lower intra-day glycemic variability and more favorable values of glycated hemoglobin and mean daily glycemia. Independent evidence indicates that strategies capable of stabilizing the glycemic profile can also reduce exposure to hypoglycemia. This conclusion is moderately supported, but it does not prove that reducing post-meal spikes alone causes such benefits in every person or in every therapeutic regimen.

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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