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ORIGINAL RESEARCH

Relative contributions of preprandial and postprandial glycemic exposures, glycemic variability, and non-glycemic factors to HbA1c in people with and without diabetes - A review of the evidence

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1. ABSTRACT

The analyzed study evaluated how pre-meal blood glucose, post-meal blood glucose, glycemic fluctuations, and certain biological factors not directly related to glucose contribute to glycated hemoglobin (HbA1c), an indicator of average blood glucose levels over the previous two to three months. The analysis used data from 77 people without diabetes and 97 people with type 2 diabetes not treated with insulin, who underwent continuous glucose monitoring.In people without diabetes, post-meal glucose exposure contributed more to the portion of HbA1c explained by the measures considered than preprandial blood glucose and glycemic variability. In type 2 diabetes, however, pre-meal and post-meal blood glucose had similar contributions, especially with higher HbA1c levels. This result contributes to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, according to which HbA1c and average blood glucose do not fully describe daily glucose dynamics. Independent studies confirm that the relative weight of postprandial and basal blood glucose changes with metabolic control and that individual biological characteristics can modify HbA1c even with the same glucose levels. However, differences between studies remain, particularly regarding the specific contribution of glycemic variability.

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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 HbA1c depends primarily on pre-meal glycemia, post-meal spikes, daily fluctuations, or non-glycemic personal characteristics. The hypothesis was that these components do not carry the same weight in people without diabetes versus those with type 2 diabetes.The research is relevant to paragraph 3.1 because it uses continuous glucose monitoring, or CGM (a technology that repeatedly records glucose levels throughout the day and night), to show elements that a single HbA1c cannot visualize: post-meal exposure, nighttime levels, and the amplitude of fluctuations. The specific point made is that the relationship between HbA1c and the glycemic profile changes based on metabolic status and that, in normoglycemic individuals, a significant portion of the differences in HbA1c is not explained by the observed glucose values.As an observational study, the research can describe associations and estimate the share of statistical variability explained by the recorded measurements. It cannot prove that a single glycemic excursion causes a specific HbA1c value, nor that reducing post-meal spikes prevents diabetes or cardiovascular complications.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The analysis used data from the multicenter ADAG study, conducted in 11 centers across the United States, Europe, Africa, and Asia between January 2006 and March 2008. After the planned exclusions, 77 participants without diabetes and 97 people with type 2 diabetes not treated with insulin were included. The latter were further divided into 63 people with HbA1c below 6.5% and 34 with HbA1c equal to or greater than 6.5%.Participants without diabetes had no family history of diabetes and had a fasting plasma glycemia no higher than 5.4 mmol/L. People with diabetes were required to have stable control over the previous six months. People treated with insulin were excluded; the text also reports that anemia and severe liver or kidney disease were exclusion criteria in the ADAG study, to limit conditions capable of altering HbA1c independently of glucose.The blinded CGM recorded glucose every five minutes for at least two days at baseline and for at least two days every four weeks during the following twelve weeks. During the monitoring periods, participants performed eight daily capillary measurements: before and 90 minutes after breakfast, lunch, and dinner, at bedtime, and at 3 a.m. The median number of days with valid CGM data was 13, with a range of 3 to 19 days.The researchers calculated pre-breakfast glycemia, nocturnal glycemia, the area under the glucose curve in the two hours after meals, the maximum peak, and several indices of variability. Among these, the standard deviation measures how much values deviate from the mean; the coefficient of variation relates this dispersion to the mean glycemia; the MAGE quantifies the amplitude of major glycemic excursions. The primary outcome was HbA1c measured after twelve weeks, as the average of four standardized analytical methods. Associations were estimated using linear regressions, first simple and then adjusted for age, sex, body mass index, and ethnicity.

4. RESULTS

The first useful finding for the reader is that glycemic values and fluctuations were higher when moving from people without diabetes to those with type 2 diabetes and higher HbA1c levels. Fasting blood glucose before breakfast averaged 5.8 mmol/L in those without diabetes, 7.2 mmol/L in the group with HbA1c below 6.5%, and 8.6 mmol/L in the group with HbA1c equal to or greater than 6.5%. The maximum glucose peak also increased: 8.9, 12.0, and 16.3 mmol/L, respectively.The eight glycemic measures considered were all associated with HbA1c across all participants, with a P-value of less than 0.001. However, the significance of the association varied between groups. In people without diabetes, after adjusting for age, sex, body mass index, and ethnicity, only the total area under the glucose curve after meals remained statistically significantly associated with HbA1c. An increase of one standard deviation in this postprandial exposure corresponded to approximately 2 mmol/mol, or 0.2 percentage points, more in HbA1c.In type 2 diabetes with HbA1c below 6.5%, more glycemic indicators remained associated with HbA1c; the most marked relationships concerned nocturnal glycemia and total postprandial area. In the group with HbA1c equal to or greater than 6.5%, fasting blood glucose before breakfast, nocturnal glycemia, postprandial area, glycemic peak, and glucose standard deviation remained associated with HbA1c even after

adjustment. In this group, an increase of one standard deviation in glycemic measures could correspond to an increase of up to 9 mmol/mol in HbA1c.The estimation of the proportions of explained variability clarifies the passage cited in the book. Without diabetes, all included variables explained 35% of the variability in HbA1c; pre-meal glycemia, postprandial glycemia, and glycemic variability explained 4%, 8%, and 7% respectively, while non-glycemic factors accounted for about half of the explained portion. In type 2 diabetes with HbA1c below 6.5%, the model explained 49% of the variability: 13% attributable to pre-meal glycemia, 17% to postprandial glycemia, and 13% to glycemic variability. With HbA1c equal to or greater than 6.5%, the model explained 78%; pre-meal and postprandial glycemia both contributed about 27%, while glycemic variability contributed 20%.

5. INTERPRETATION

In simple terms, HbA1c is not a precise record of every single glucose spike or drop. It is a summary measure of glycemic exposure over time. Two people with similar HbA1c levels can therefore have different daily patterns, because one may have relatively stable values while the other alternates between post-meal rises and more rapid reductions.The segment documented by the analyzed study is as follows: in people without diabetes, total glucose exposure in the two hours after meals was the glycemic determinant most closely associated with HbA1c; in type 2 diabetes, pre-meal and post-meal glycemia contributed to a similar extent, especially with higher HbA1c. The study also documents that age, sex, body mass index, and ethnicity explained a relatively more significant portion of HbA1c variability in people without diabetes.This does not mean that postprandial glycemia is the only cause of HbA1c in people without diabetes, nor that glycemic variability lacks clinical importance. Glycemic measures were correlated with each other; furthermore, physical activity and diet were not recorded during the CGM periods. The authors also note that using pre-breakfast glycemia as a reference value could underestimate actual postprandial exposure and overestimate preprandial exposure.

6. INDEPENDENT CONFIRMING EVIDENCE

An independent analysis conducted on 290 people with type 2 diabetes not treated with insulin confirms the concept that the relative contribution of blood glucose after meals is not fixed along the continuum of metabolic control. In the lowest HbA1c quintiles, the postprandial increase contributed to 69.7% of the estimated daytime hyperglycemia, while in the highest HbA1c quintile, it contributed to 30.5%; conversely, the share attributed to fasting glycemia increased from 30.3% to 69.5%. This observational study does not measure the same set of metrics as the analyzed work, but it confirms that the postprandial component is relatively more relevant when control is better and that the basal component grows as hyperglycemia worsens [1].The section of the book regarding biological factors not directly attributable to glucose values is supported by a study on healthy twins and twins with type 1 diabetes. In healthy subjects, a genetic model attributed 62% of the variability of HbA1c to additive genetic effects, with a 95% confidence interval from 47% to 75%. The authors noted that this heritability was not explained by genes shared with fasting glycemia. This is an observational confirmation of the presence of non-glycemic components, but it does not demonstrate which genes or mechanisms are responsible in each individual [2].A second independent study provided a concrete biological explanation: the lifespan of red blood cells. In six people with diabetes and six controls without diabetes, the lifespan of red blood cells was measured using biotin labeling. The average age of the cells ranged from 39 to 56 days in participants with diabetes and from 38 to 60 days in the controls. This heterogeneity was sufficient to produce clinically relevant differences in HbA1c given the same average glycemia. The result confirms that HbA1c reflects glucose, but also the time for which hemoglobin remains exposed to glucose inside the red blood cells [3].Taken together, these publications do not repeat the ADAG protocol, but they converge on the two central elements of the narrative: the weight of the preprandial and postprandial components changes with the level of glycemic control, and HbA1c contains an individual biological component that does not perfectly coincide with the glycemic profile detected by CGM.

7. CONFLICTING EVIDENCE

A study conducted on 63 people with well-controlled type 2 diabetes, with HbA1c below 7.0%, introduces an important limitation. Using CGM and a standardized meal, the authors observed that HbA1c was associated with the overall magnitude of hyperglycemia, but did not correlate with MAGE or the standard deviation score. In the multivariate model, only fasting glycemia predicted HbA1c, with an R^2 of 0.24; postprandial glycemia from the standardized meal, duration of hyperglycemia, and variability indices did not add statistically significant predictive value [4].This result does not invalidate the correspondence between the original study and the book's paragraph. Instead, it shows that the relationship between HbA1c, post-meal spikes, and variability depends on the measurement method, the duration of monitoring, the definition of postprandial, and the population studied. The conflicting study was smaller, included exclusively people with well-controlled type 2 diabetes, and cannot establish that variability indices are biologically irrelevant; however, it indicates that HbA1c may not reliably capture such fluctuations.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent evidence used to confirm or define the scope of the paragraph's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Multicenter observational with repeated CGM	77 people without diabetes and 97 with type 2 diabetes not treated with insulin	In those without diabetes, postprandial exposure explained more HbA1c variability than preprandial glycemia and variability; in type 2 diabetes, preprandial and postprandial contributions were similar.	direct confirmation	moderate
[1]	Cross-sectional observational	290 people with type 2 diabetes not treated with insulin or acarbose	With lower HbA1c, the relative postprandial share was higher; with higher HbA1c, the relative share of fasting glycemia increased.	direct confirmation	moderate
[2]	Observational twin study	Healthy twins without diabetes and twin pairs with type 1 diabetes	Additive genetic effects explained 62% of HbA1c variability in healthy twins and did not coincide with those of fasting glycemia.	indirect confirmation	moderate

[3]	Experimental physiological study in humans	6 people with diabetes and 6 controls without diabetes	Differences in red blood cell survival could cause clinically relevant differences in HbA1c at the same mean glycemia.	biologically consistent evidence	moderate
[4]	Observational study with CGM and standardized meal	63 people with well-controlled type 2 diabetes	HbA1c was predicted by fasting glycemia, but not by MAGE, standard deviation, or postprandial glycemia from the test.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports the use of CGM to distinguish between pre- and post-meal glycemic exposure, daily fluctuations, and HbA1c. In individuals without diabetes, postprandial exposure was the most significant glycemic determinant of HbA1c; in type 2 diabetes, preprandial and postprandial glycemia contributed to a similar extent.The book's narrative is confirmed by independent evidence: the relative contribution of postprandial glycemia tends to be greater with lower HbA1c, while the weight of fasting glycemia increases as glycemic control worsens. It is also well-supported that HbA1c can be influenced by non-glycemic biological factors, including the lifespan of red blood cells. The quantitative role of glycemic variability in relation to HbA1c, however, remains context-dependent and requires cautious interpretation.

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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