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ORIGINAL RESEARCH

Glycemic variability parameters in continuous glucose monitoring as predictors of diabetes: a prospective evaluation in a non-diabetic general population - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether certain glycemic variability indices derived from continuous glucose monitoring could anticipate the onset of type 2 diabetes in individuals who were initially non-diabetic. Among 497 participants followed for approximately six years, 25 developed diabetes. At enrollment, these individuals exhibited higher mean glucose, fasting glycemia, glycated hemoglobin, and glycemic fluctuations. Among the indices analyzed, the standard deviation of blood glucose showed the best discriminatory capacity.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the idea that the loss of glycemic stability may be an early sign of metabolic deterioration. Independent evidence shows that variability increases during the transition from normal glucose regulation to diabetes and is associated with reduced pancreatic beta-cell function. Controlled experiments also support a possible biological effect of fluctuations on oxidative stress and endothelial function. However, larger prospective studies, with analyses adjusted for conventional risk factors, are still needed before these parameters can be used as standalone diagnostic tools.

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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 daily glucose fluctuations, measured before diagnosis, were associated with the subsequent development of type 2 diabetes. The hypothesis was that less stable glycemia, even in people who did not yet have diabetes, could identify an early phase of loss of glucose homeostasis, i.e., the body's ability to maintain glucose within physiological ranges.The research is relevant to sections 3.1 and 14.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it precisely documents the prospective segment of the narrative: people who were initially non-diabetic who, years later, received a diagnosis of diabetes already had wider glycemic fluctuations at baseline. However, the work does not prove that these fluctuations are the cause of diabetes, nor that correcting them prevents the disease. Furthermore, it does not establish that variability adds independent predictive value compared to fasting glycemia, glycated hemoglobin, body weight, and other risk factors, as multivariate models for such a comparison are not reported in the available material.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is a prospective analysis of the AEGIS population cohort, which began in Spain in 2012. Of the 1,516 initial participants, 622 agreed to continuous glucose monitoring, and 497 were included in the statistical analysis. Exclusions included, among others, subjects with previously diagnosed diabetes, fasting glycemia equal to or greater than 126 mg/dL, glycated hemoglobin equal to or greater than 6.5%, pregnancy, acute illness, chronic kidney or liver disease, and medications known to affect glucose metabolism.Participants wore an iPro2 subcutaneous sensor for seven consecutive days, maintaining their usual dietary and physical activity habits. Days with incomplete data or a discrepancy of more than 18% between the sensor and capillary measurements were excluded. At least two full days of recording were required for each participant; in total, 2,347 days were analyzed. The sensor provided a repeated measure of glucose during daily life, rather than the single snapshot offered by fasting glycemia.The standard deviation, which expresses how much values deviate on average from the mean glycemia; the coefficient of variation, which relates this dispersion to the mean; and the MAGE, or the mean amplitude of glycemic excursions, were calculated. Subsequent diagnosis of diabetes followed the American Diabetes Association criteria. The median follow-up was approximately six years, with an interquartile range of 4.9 to 7.3 years. Differences between groups were evaluated using Student's t-tests or Mann-Whitney tests; the discriminative capacity of the metrics was examined using ROC curves, which are analyses that estimate how well an indicator separates those who will develop an event from those who will not.

4. RESULTS

During the follow-up, 25 of the 497 participants developed type 2 diabetes: 16 out of 324 women, equal to 4.9%, and 9 out of 173 men, equal to 5.2%. No significant differences emerged between men and women in the proportion of new diagnoses. This limited number of events is important: it allows for the observation of an association, but it reduces the precision with which predictive thresholds applicable to the general population can be defined.People who developed diabetes already had less favorable glucose regulation at the start of the study. Their average glycated hemoglobin was 5.8% compared to 5.3% in the 472 participants who remained diabetes-free, while fasting glycemia was 102 compared to 86 mg/dL; for both differences, the P-value was less than 0.001. They also had a higher average glycemia recorded by the sensor, 115 versus 105 mg/dL, with a P-value of less than 0.001.Fluctuations were also greater in the group that developed diabetes. The standard deviation was 18.4 versus 13.3 mg/dL, the coefficient of variation 16.9% versus 14.4%, and the MAGE 35.9 versus 27.4 mg/dL. The differences were statistically significant: P less than 0.001 for standard deviation and MAGE, and P equal to 0.004 for the coefficient of variation. In simple terms, before their future diagnosis, these people did not just show higher average values, but also wider increases and decreases in glucose.In the ROC analysis, the standard deviation was the index with the best discriminatory capacity in the entire cohort, with an area under the curve of 0.81 and a 95% confidence interval from 0.73 to 0.88. An area under the curve of 0.81 indicates good discrimination in the studied sample, but it is not equivalent to a certain

diagnosis for the individual. The threshold value of 14.9 mg/dL achieved a sensitivity of 80%, meaning it identified 80 out of 100 people who would develop diabetes, and a specificity of 72.3%, meaning it correctly classified about 72 out of 100 people who would not develop it. The coefficient of variation and MAGE showed lower discriminatory capacities compared to the standard deviation.

5. INTERPRETATION

The main takeaway is that unstable glycemia can be observed before a clinical diagnosis of diabetes. This result is consistent with the idea that glucose regulation gradually loses precision: after meals, levels may rise higher, return to baseline more slowly, or fluctuate more significantly throughout the day.The segment directly documented by the publication subject to the Evidence Review is therefore: greater glycemic variability measured by continuous monitoring at the start of the study higher subsequent frequency of diabetes diagnosis in the same cohort. Standard deviation, coefficient of variation, and MAGE are quantitative markers of this instability; they are not, in themselves, a biological explanation of the disease.The data do not allow for a complete separation of the contribution of these oscillations from that of an already higher mean glycemia, fasting glycemia, glycated hemoglobin, or other metabolic factors. In other words, instability could be an early signal of the same deterioration that leads to diabetes, rather than an independent cause. The proposal contained in the book's paragraph suggesting that oscillations may contribute to disease progression therefore requires an additional chain of biological and experimental evidence.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the progression of variability along the metabolic continuum comes from a cross-sectional study of 162 people: 53 with normal glucose tolerance, 53 with impaired glycemic regulation, and 56 with newly diagnosed type 2 diabetes, not treated with medication. After three days of continuous monitoring, the groups with impaired glycemic regulation and diabetes showed higher standard deviation and MAGE compared to the normoglycemic group. In the diabetes group, variability between consecutive days and post-meal excursions were also greater. This study confirms that increased oscillations are already detectable in the pre-diabetic or early stages of diabetes, but its cross-sectional design cannot establish which alteration appears first [1].A second independent study further explored the pathophysiological link suggested in chapter 3. In 220 people ranging from normal glucose regulation to newly diagnosed diabetes, all monitored for 72 hours and subjected to a 75 g oral glucose tolerance test, standard deviation, MAGE, and other indices increased progressively as the oral disposition index decreased. This index combines insulin secretion and insulin sensitivity and is used as an estimate of the compensatory capacity of pancreatic beta cells. In the entire sample, MAGE and standard deviation showed an inverse correlation with this index, r=-0.65 and r=-0.66 respectively, with P less than 0.001. The result supports the association between glycemic instability and worse beta-cell function, without demonstrating that higher variability directly causes beta-cell damage [2].The possible biological pathway proposed in chapter 14, i.e., repeated oscillations oxidative stress and endothelial dysfunction, receives support from a controlled experiment in humans. In normoglycemic subjects and people with type 2 diabetes, a hyperglycemic clamp compared constantly high glucose levels with oscillations between 5 and 15 mmol/L every six hours for 24 hours. The oscillations produced a greater increase in markers of oxidative stress and a greater worsening of flow-mediated dilation, an indicator of the vessels' ability to relax. The experimental model strengthens the biological plausibility of the effect of oscillations, but the short duration and artificial context do not prove that this mechanism causes diabetes in daily life [3].

7. CONFLICTING EVIDENCE

A systematic review and meta-analysis of 71 studies conducted in people without diabetes confirmed that many measures of glycemic variability are higher in prediabetes and that variability appears to be inversely associated with beta-cell function. However, the authors noted that most studies were cross-sectional and that the association of variability with insulin sensitivity, adiposity, blood pressure, lipids, hepatic steatosis, and oxidative stress remained unclear. They also concluded that more prospective

studies are needed to define its predictive power regarding incident diabetes [4].This evidence does not directly contradict the AEGIS result, but it scales back the broader interpretation: glycemic variability is a promising indicator of impaired metabolic regulation, but it is not yet a standardized prognostic marker nor a proven causal target in the population without diabetes. No directly conflicting evidence of sufficient relevance was identified; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the prospective data from the original study from independent evidence that confirms individual steps of the narrative and from the review that defines its limitations.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Prospective cohort	497 initially non-diabetic adults, followed for approximately six years	Those who developed diabetes had higher baseline SD, CV, and MAGE; SD had an AUC of 0.81.	direct confirmation	moderate
[1]	Cross-sectional observational	162 people with normal tolerance, impaired glycemic regulation, or newly diagnosed diabetes	SD and MAGE increased from normal homeostasis to impaired regulation and diabetes.	indirect confirmation	moderate
[2]	Cross-sectional observational	220 people across different stages of glucose tolerance	Variability indices increased while the oral disposition index decreased.	indirect confirmation	moderate
[3]	Controlled human experimental	Normoglycemic subjects and people with type 2 diabetes undergoing glucose clamp	Glucose oscillations increased oxidative stress and endothelial dysfunction more than stably elevated glycemia.	biologically consistent evidence	moderate
[4]	Systematic review and meta-analysis	71 studies on people without diabetes	Higher variability in prediabetes, but prospective evidence and links with many cardiometabolic factors remain uncertain.	neutral evidence	high

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports the observation that individuals initially without diabetes, but with wider glycemic variability, developed type 2 diabetes more frequently over approximately six years of observation. The standard deviation showed the best discriminatory capacity in the sample. Independent evidence confirms that variability increases along with metabolic deterioration and is associated with reduced beta-cell function. The possible causal role of fluctuations through oxidative stress and vascular dysfunction is supported primarily at the experimental level. The use of continuous monitoring to predict or prevent diabetes in the general population still requires clinical validation and shared thresholds.

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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