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Early beta-cell dysfunction versus insulin hypersecretion as a primary event in the pathogenesis of dysglycemia - Review of the evidence

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1. ABSTRACT

The publication analyzed is a narrative review comparing two models to explain the origin of dysglycemia, i.e., the abnormal increase in glycemia: early pancreatic beta-cell dysfunction or primary insulin hypersecretion. The authors conclude that the former model is supported by the majority of the clinical, genetic, experimental, and interventional evidence considered. As only the abstract is available, the search strategy, number of studies included, selection criteria, and quantitative analyses are not reported in the available material.In section 3.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that hyperglycemia appears when insulin secretion can no longer adequately compensate for insulin resistance. Independent prospective studies show that lower beta-cell function corrected for insulin sensitivity predicts future diabetes. However, some observational data indicate that primary insulin hypersecretion may characterize specific subgroups; the most prudent conclusion is therefore that the early dysfunction model is well-supported, but not universally exclusive.

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 which alteration appears first in the majority of people who develop type 2 diabetes: a reduced capacity of pancreatic beta cells to adapt insulin secretion to demand, or an excessive production of insulin that precedes and promotes insulin resistance, obesity, and subsequent pancreatic exhaustion.The distinction is important because a high blood insulin level does not automatically equate to effective pancreatic function. If tissues respond poorly to insulin, the pancreas must produce more to keep glycemia stable. Beta-cell function must therefore be interpreted in relation to insulin sensitivity, not as an absolute quantity of insulin.The relevance to the book's section is precise: the publication examines whether the loss of the compensatory capacity of beta cells is an initial and determining step in dysglycemia. However, it cannot prove that this is the first event in every individual, because it is a review of different studies and because type 2 diabetes and prediabetes include biologically heterogeneous subgroups.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is a narrative review of the literature. The abstract reports that the authors discussed preclinical, clinical, and interventional data in the context of two opposing pathophysiological models: early beta-cell dysfunction or primary beta-cell hyperstimulation with insulin hypersecretion.Since the available material contains only the abstract, the following information is not reported in the available material: databases consulted, search terms, period covered, inclusion and exclusion criteria, number of publications examined, risk of bias assessment, population characteristics, statistical methods, and the presence of a meta-analysis. Therefore, no verifiable aggregated quantitative results are available.The work is neither a clinical trial nor an original cohort study. Its strength lies in integrating different lines of research; its limitation is that, without the full text being accessible, it is not possible to evaluate in detail how the individual pieces of evidence were weighted.

4. RESULTS

The main result reported in the abstract is that the majority of available data supports the model of early functional beta-cell dysfunction as the most likely mechanism underlying hyperglycemia in most people who develop type 2 diabetes. In simple terms, the problem is not just how much insulin is present in the blood, but whether the pancreas can increase it appropriately when glucose levels rise and when tissues become less sensitive to its effect.The authors acknowledge an alternative model: primary stimulation of beta-cells could cause insulin hypersecretion, subsequently contribute to obesity and insulin resistance, and eventually lead to functional exhaustion. The abstract does not report how many studies favor each model, nor does it provide effect sizes, confidence intervals, or P-values. These data are not reported in the available material.The segment most relevant to the book is therefore the following: in the presence of insulin resistance, hyperglycemia becomes more likely when insulin secretion no longer increases sufficiently in relation to metabolic demand. The study does not state that insulin resistance is irrelevant; rather, it states that, on its own, it does not explain why some people maintain normal glycemia while others progress toward dysglycemia.

5. INTERPRETATION

The biological interpretation is that beta cells function as an adaptive system. When the body requires more insulin, for example in the presence of increased adiposity or reduced tissue sensitivity, an efficient pancreas increases secretion proportionally. If this increase does not occur or is delayed, a greater amount of glucose remains in the blood.The parameter that represents this concept is the disposition index: it combines a measure of insulin secretion with a measure of insulin sensitivity. A reduction in this index suggests that the pancreatic response no longer adequately compensates for insulin resistance. However, it does not identify a single biological cause on its own, nor does it allow for establishing with certainty when the defect began.Regarding the section from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication primarily supports the interpretation that dysglycemia

emerges when beta-cell compensation fails. This is a conceptual and pathophysiological support, not an experimental demonstration of a single temporal sequence valid for all individuals.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial independent confirmation comes from a prospective study of 400 adults without diabetes at baseline, followed for approximately ten years. The researchers calculated an oral disposition index, defined as the product of the early insulin response to an oral glucose load and a measure of insulin sensitivity. The index decreased as participants progressed from normal glucose tolerance to dysglycemia and diabetes. A lower baseline value predicted the development of diabetes even after adjusting for age, sex, body mass index, family history, fasting glycemia, and two-hour glycemia. This result directly supports the idea that insufficient beta-cell compensation precedes clinically recognizable hyperglycemia [1].A second prospective cohort, the Insulin Resistance Atherosclerosis Study, used more direct measures of insulin sensitivity and early insulin response via an intravenous glucose tolerance test with repeated sampling. Among 826 participants aged 40-69, 128 people, or 15.5%, developed diabetes after five years. After adjusting for glycemia, adiposity, family history, and demographic characteristics, a one-standard-deviation increase in the disposition index was associated with lower odds of developing diabetes: odds ratio 0.68, 95% confidence interval 0.54-0.85. Since the value is less than one, it indicates a reduction in the probability of the event with better beta-cell compensation [2].These two studies do not prove that the beta-cell defect is always the primary causal event. However, they show, in populations followed over time, that an inadequate insulin response relative to insulin sensitivity more frequently precedes and predicts the progression toward diabetes. This convergence is particularly relevant to the phrase in the book that distinguishes absolute insulinemia from the pancreas's actual capacity to meet metabolic demand.

7. CONFLICTING EVIDENCE

There is relevant data suggesting that the model of early dysfunction should not be considered universal. In a prospective cohort of women evaluated after pregnancy and followed up with oral glucose tolerance tests, higher post-load insulin levels were not associated with a subsequent worsening of cardiometabolic indicators. The authors concluded that post-prandial insulin elevation alone does not necessarily identify an unfavorable metabolic effect and does not, by itself, justify the idea that it must be reduced to achieve a benefit [3].This evidence does not refute the role of beta-cell dysfunction. Rather, it shows that insulin concentration after glucose intake may reflect a compensatory response, differences in hepatic insulin clearance, or specific characteristics of the study population. Hyperinsulinemia must therefore be interpreted in conjunction with glycemia, insulin sensitivity, and beta-cell function, not as independent proof of disease or causality.No sufficiently relevant directly conflicting evidence has been identified to demonstrate that, under the same conditions, primary hypersecretion is the predominant mechanism in the majority of people; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the narrative progression of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Synthesis of preclinical, clinical, and intervention studies	The majority of the evidence considered favors early beta-cell dysfunction over primary hypersecretion as an explanation for dysglycemia.	biologically consistent evidence	moderate
[1]	Prospective observational	400 adults without diabetes at baseline, followed for approximately ten years	A lower oral disposition index predicted future diabetes independently of baseline glycemia and major risk factors.	direct confirmation	moderate
[2]	Prospective observational	826 adults aged 40-69; five-year follow-up	A higher disposition index was associated with lower odds of conversion to diabetes, even after adjustments.	direct confirmation	moderate
[3]	Prospective observational	Women followed after pregnancy with repeated oral glucose tolerance tests	Higher insulinemia after glucose intake showed no adverse cardiometabolic implications at follow-up.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the thesis that dysglycemia primarily appears when beta cells can no longer adequately compensate for insulin resistance. Available independent cohorts confirm that a reduced disposition index predicts future diabetes even before clinical diagnosis.This conclusion does not imply that hyperinsulinemia is always harmful, nor that beta-cell dysfunction is the only possible initial event. The most robust interpretation is that type 2 diabetes and prediabetes are heterogeneous: in the majority of cases, the loss of pancreatic compensation is well-supported, while the precise order of events requires further longitudinal and mechanistic validation.

Aggiornato al 24/11/2026. 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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