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ORIGINAL RESEARCH

Beta-cell dysfunction and glucose intolerance: results from the San Antonio Metabolism (SAM) study - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether the function of pancreatic beta cells, the cells that produce insulin, changes during the transition from normal glucose tolerance to glucose intolerance and type 2 diabetes. In 388 adults, researchers compared the insulin response after an oral glucose load with insulin sensitivity measured by euglycemic clamp, a gold-standard procedure for estimating how effectively the body responds to insulin.Beta-cell function, adjusted for insulin resistance, decreased progressively as two-hour glycemia increased, including within ranges formally compatible with normal glucose tolerance. This finding contributes to the perspective from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which suggests that pancreatic impairment may be recognizable before reaching the diagnostic thresholds for prediabetes and diabetes. Independent studies in obese youth, adults without diabetes, and women followed longitudinally show a consistent picture: higher blood glucose levels, even in non-diabetic ranges, are associated with a lower compensatory capacity of beta cells. However, there are differences between populations and measurement methods; insulin resistance may play a predominant role in some contexts. Overall, the narrative is moderately confirmed, but it does not prove that a single slightly elevated blood glucose level inevitably leads to diabetes.

ONLINE ARTICLE

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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 at what level of glycemia a reduction in pancreatic beta-cell function becomes detectable, while simultaneously considering insulin resistance. This clarification is important: a high amount of insulin in the blood does not guarantee that the pancreas is responding adequately, because an insulin-resistant person requires more insulin to keep glycemia under control.The study therefore evaluated whether the insulin response to glucose was proportional to both the increase in glycemia and the degree of insulin resistance. This is relevant to paragraph 3.2 because it documents the core of the narrative: along the spectrum ranging from normal glucose tolerance to type 2 diabetes, the adaptation of beta cells decreases progressively; this reduction is already observable in some people who are formally glucose-tolerant.The research is cross-sectional: it compares groups evaluated at a specific moment in time, without following them over time. It can therefore describe an association between higher glycemia and lower beta-cell function corrected for insulin resistance, but it cannot prove that the glycemic increase is the cause of the dysfunction, nor can it estimate an individual's future risk of diabetes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract. The study included 388 participants from the San Antonio Metabolism study: 138 with normal glucose tolerance, 49 with impaired glucose tolerance, and 201 with type 2 diabetes. Glucose tolerance was assessed using an OGTT (oral glucose tolerance test), which measures how glycemia and insulin change after the intake of glucose.Insulin sensitivity was estimated using a hyperinsulinemic-euglycemic clamp, a technique in which insulin is administered in a controlled manner and glucose is adjusted to keep glycemia stable. In simple terms, it allows for the quantification of how much glucose the body can utilize in response to insulin.The authors calculated the ΔI/ΔG/IR index: the increase in insulin relative to the increase in glucose during the OGTT, divided by the insulin resistance measured via clamp. This index expresses a pancreatic response adapted to both the glycemic stimulus and the insulin requirement. The abstract reports comparisons between lean and obese subjects and between two-hour glycemia categories. Inclusion and exclusion criteria, recruitment period, distribution by sex and age, detailed statistical analyses, and numerical values of the index are not reported in the available material.

4. RESULTS

The main result was a progressive decline in the insulin secretion index adjusted for insulin resistance as glycemia increased two hours after the OGTT. In simple terms, in people with higher post-load glycemia, the pancreas provided an insulin response that was less adequate for metabolic needs.In lean participants with normal glucose tolerance, the ΔI/ΔG/IR index was progressively lower in groups with two-hour glycemia between 5.6 and 6.6 mmol/L and between 6.7 and 7.7 mmol/L, compared to those with values below 5.6 mmol/L. These ranges correspond approximately to 101-119 mg/dL and 121-139 mg/dL. A further reduction in the index was observed in impaired glucose tolerance, with values between 7.8 and 11.0 mmol/L, and in type 2 diabetes, with values above 11.1 mmol/L.Lean and obese participants showed overlapping trends in the relationship between two-hour glycemia and the ΔI/ΔG/IR index. The data relevant to the book is therefore the continuous direction of the association: higher post-load glycemia corresponded to lower estimated beta-cell function in relation to insulin resistance. The abstract does not report absolute index values, confidence intervals, P-values, or analyses adjusted for other factors.

5. INTERPRETATION

Beta cells function as a compensation system. When muscles, the liver, and adipose tissue respond less to insulin, the pancreas must appropriately increase insulin secretion to keep glycemia within non-diabetic limits. The study suggests that this compensation becomes progressively less effective as post-load glycemia increases.The segment directly documented by the publication subject to the Evidence Review is: higher two-hour glycemia during OGTT lower insulin response corrected for insulin resistance. It does not directly demonstrate the physical loss of beta cells, nor does it establish the chronological sequence in which insulin resistance and pancreatic dysfunction appear in an individual.This distinction helps in

understanding the book's paragraph. Elevated insulinemia may represent a compensatory attempt rather than proof of preserved pancreatic function. However, since the research is cross-sectional and the available information is limited to the abstract, the result should be interpreted as a robust pathophysiological association within the studied sample, not as a diagnostic threshold valid for everyone, nor as a demonstration of causality.

6. INDEPENDENT CONFIRMING EVIDENCE

Confirmation particularly relevant to the early part of the narrative comes from a study of 407 obese children and adolescents with normal glucose tolerance. As the two-hour glycemia increased from less than 100 mg/dL to 100-119 mg/dL and then to 120-139 mg/dL, glycemia in the first 30 minutes of the OGTT increased progressively, while the increase in insulin did not grow proportionally. Consequently, the insulinogenic index, a measure of the pancreas's early response, decreased. The result remained observable at different levels of insulin sensitivity, supporting the idea that beta-cell response may be less effective even within the range of normal glucose tolerance [1]. The study is cross-sectional, concerns obese youth, and cannot be automatically extended to adults or people with different adiposity levels.A second study examined 531 adults without diabetes, including 293 with normal tolerance and 238 with impaired glucose tolerance, belonging to Japanese and Mexican-American populations. As fasting glycemia increased from 70 to 125 mg/dL, the insulin secretion index adjusted for insulin resistance decreased exponentially; every 28 mg/dL increase was associated with a 63% reduction in the index. The association primarily concerned early secretion, within the first 30 minutes. This confirms, on a different glycemic axis, the concept that even non-diabetic increases in glycemia can be accompanied by a lower pancreatic compensatory capacity [2]. The analysis remains observational and does not allow for the complete separation of cause, consequence, and possible shared factors.The most relevant longitudinal evidence comes from 302 women with normal glucose tolerance three months postpartum, re-evaluated at one, three, and five years. Eighty-nine developed prediabetes or diabetes. From the beginning, the future participants who progressed had higher fasting and two-hour glycemia, greater insulin resistance, and lower beta-cell function. During follow-up, the worsening of the ISSI-2, an index that integrates insulin secretion and sensitivity, proved to be the most important determinant of progression; its contribution to predictive capacity was greater than that of insulin resistance indices [3]. The sample is specific to women in the postpartum period, and the result does not prove that beta-cell dysfunction alone explains all cases of dysglycemia.

7. CONFLICTING EVIDENCE

A more cautious interpretation comes from the multicenter RODAM study, conducted on 4,079 Ghanaian adults without diabetes living in Ghana or Europe. To explain the geographical differences in impaired fasting glycemia, the authors estimated insulin resistance and beta-cell function using HOMA-IR and HOMA-B, indices derived from fasting glycemia and insulin. A one-standard-deviation increase in HOMA-IR explained an attributable fraction of 69.3% of the condition, compared to 11.1% attributed to beta-cell dysfunction estimated via HOMA-B [4].This evidence does not negate the result of the original study, but it shows that the relative weight of the two processes may depend on the population, the glycemic parameter considered, and the method used to measure pancreatic function. The RODAM study is cross-sectional, focuses on fasting glycemia, and uses surrogate measures rather than the clamp technique or dynamic response after glucose intake. Therefore, it limits the generalizability of the idea that beta-cell reduction is always the predominant factor, without undermining the consistency of the relationship observed after an oral glucose load.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the Evidence Review from independent publications that confirm or define the scope of the narrative in the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cross-sectional study with OGTT and euglycemic clamp	388 adults: normal tolerance, impaired tolerance, and type 2 diabetes	As two-hour glycemia increased, the insulin secretion index adjusted for insulin resistance decreased, even in those with normal tolerance	direct confirmation	moderate
[1]	Cross-sectional observational study	407 obese children and adolescents with normal glucose tolerance	Higher two-hour glycemia within the normal range was associated with a reduction in the insulinogenic index, regardless of insulin sensitivity levels	direct confirmation	moderate
[2]	Cross-sectional observational study	531 Japanese and Mexican-American adults without diabetes	Higher fasting glycemia was associated with a reduction in the insulin secretion index adjusted for insulin resistance, especially in the early phase	indirect confirmation	moderate
[3]	Longitudinal observational study	302 normoglycemic women three months postpartum, followed for five years	Deterioration of beta-cell function indices was the main determinant of progression toward prediabetes or diabetes	indirect confirmation	moderate
[4]	Multicenter cross-sectional observational study	4,079 adults from Ghana without diabetes living in Ghana or Europe	In the geographic differences of impaired fasting glycemia, estimated insulin resistance explained a greater share of the estimated beta-cell dysfunction	conflicting evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The SAM study directly supports the idea that beta-cell function, when assessed in relation to glycemia and insulin resistance, progressively declines from normal glucose tolerance to type 2 diabetes. Independent evidence makes this narrative moderately supported, including the observation that certain alterations may be recognizable before diagnostic thresholds are reached.

The conclusion, however, requires caution. The data do not demonstrate that a mild elevation in glycemia alone causes diabetes, nor that beta-cell dysfunction carries the same weight in every person or population. Insulin resistance, adiposity, genetic context, and other mechanisms remain relevant components of metabolic progression.

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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