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ORIGINAL RESEARCH

Glucose homeostatic law: insulin clearance predicts the progression of glucose intolerance in humans - Evidence review

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1. ABSTRACT

The original study analyzed 113 people with normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes. By combining consecutive hyperglycemic and hyperinsulinemic-euglycemic clamps with a mathematical model, the authors estimated insulin sensitivity, insulin secretion, and insulin clearance, i.e., the rate at which insulin is removed from the blood. The mathematical parameter of clearance decreased in groups with worse glucose tolerance and was associated with higher glycemia after an oral glucose load.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the passage stating that insulin clearance is linked to postprandial glycemia and the deterioration of glucose tolerance. Independent studies in humans confirm that lower clearance is accompanied by insulin resistance and dysglycemia; a longitudinal cohort also associates it with the onset of dysglycemia. However, the available indices are not equivalent and do not prove that reducing clearance causes diabetes.

ONLINE ARTICLE

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MISSION

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2. ANALYZED STUDY

The research question was whether insulin clearance, in addition to pancreatic secretion and tissue sensitivity to insulin, could describe the worsening of glucose tolerance. The hypothesis was that these three processes were integrated components of the same control system and that insulin clearance decreased with the transition from normal glycemic regulation to impaired glucose tolerance and type 2 diabetes.The relevance to paragraph 2.2 is specific. The study was not designed to directly measure how much insulin the liver extracts during the first pass, nor to demonstrate that a change in clearance causes diabetes. Instead, it documents a precise segment of the narrative: in people with different levels of glucose tolerance, a modeling parameter of insulin degradation decreases in parallel with metabolic worsening and is inversely associated with glycemia after a glucose load.The work can therefore show associations between experimental measurements, model-estimated parameters, and glycemic status. It cannot establish the individual causal sequence of events, nor transform insulin clearance into a clinical biomarker already validated for predicting diabetes in an individual.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study initially included 121 adults recruited at the Kobe University Hospital between October 2008 and June 2014. Eight participants were excluded as outliers of the model parameters; the final analysis involved 113 people: 47 with normal glucose tolerance, 16 with impaired glucose tolerance, and 50 with type 2 diabetes. Detailed characteristics of the groups are reported in the supplementary material, but full clinical inclusion and exclusion criteria are not provided in the available material.Within ten days, each participant underwent an oral glucose tolerance test with 75 g of glucose and two consecutive clamps. In the hyperglycemic clamp, glycemia was maintained at 200 mg/dL for 90 minutes to primarily assess the secretory response of the pancreas. Ten minutes later, a 120-minute hyperinsulinemic-euglycemic clamp began, in which insulin was infused at 40 mU per square meter per minute and glucose was maintained at around 90 mg/dL; this procedure allows for the estimation of how effectively the body uses glucose in the presence of insulin.The authors constructed a personalized mathematical model using glucose and insulin time series. In the model, k4 represented insulin sensitivity, k5 insulin secretion, and k7 insulin clearance, defined as the rate of insulin degradation. The insulin sensitivity index, the incremental area of insulin in the first ten minutes of the hyperglycemic clamp, and the disposition index or DI—the product of secretion and sensitivity, used as an integrated indicator of the ability to control glucose—were also calculated. Comparisons between the three groups were performed using Steel-Dwass tests; P less than 0.05 was considered statistically significant.

4. RESULTS

The model reproduced the expected clinical differences between the groups. Insulin sensitivity was higher in individuals with normal glucose tolerance compared to the groups with impaired tolerance or diabetes. Early insulin secretion, however, was similar between normal and impaired tolerance, but was lower in type 2 diabetes. Consequently, the DI decreased progressively from normal tolerance to impaired tolerance and then to diabetes: in simple terms, the combination of insulin production and tissue response became less effective.The key result for the book's section concerns k7. This parameter, interpreted by the authors as the rate of insulin clearance, decreased significantly across the three groups, following the order of normal tolerance, impaired tolerance, and type 2 diabetes. The product k4×k5, considered the modeling analogue of the DI, also decreased with the same progression. The complete median values of the parameters for each group are not reported in the available material.A lower k7 value was associated with higher glycemia during the oral glucose tolerance test, including the 120-minute value, i.e., late postprandial glycemia. The authors also report that k7 showed the highest correlation with certain glucose disposal indices and with the oral DI. The association was inverse: as the clearance parameter decreased, glycemia after the load increased. The correlation coefficient for glycemia at 120 minutes is not reported in the available text; it is instead specified that the clinical MCR index, an estimate of clearance based on insulin infusion, had weak correlations with glycemia at 120 minutes,

equal to r = −0.17, and with the clamp DI, equal to r = 0.32.Finally, the model suggested an approximately quadratic mathematical relationship between k7 and the product k4×k5, with an estimated power index of 1.98. This indicates a regularity in the modeled data, not a definitively proven physiological law nor a direct causal relationship between the three processes.

5. INTERPRETATION

The general implication is that the amount of insulin present in the blood does not depend solely on how much insulin the pancreas releases. It also depends on how quickly the body, especially the liver, removes it. In the analyzed sample, a lower model-based clearance was associated with a reduced overall capacity to regulate glucose and higher postprandial glycemia.The segment documented directly by the publication subject to the Evidence Review is: worsening glucose tolerance reduction of k7, a model parameter of insulin clearance inverse association with glycemia after an oral load. The study therefore supports the idea that clearance, secretion, and insulin sensitivity are interdependent, but it does not demonstrate that reduced clearance is always the primary biological event, nor that it is, by itself, the cause of insulin resistance.There are significant limitations. The design is cross-sectional: it compares groups with different metabolic conditions at a single point in time, and therefore does not directly observe their individual progression toward diabetes. Furthermore, k7 is not a direct measure of hepatic clearance alone: it is a parameter derived from a model built on clamp data. Comparison with MCR shows that different ways of estimating clearance can provide non-overlapping information.

6. INDEPENDENT SUPPORTING EVIDENCE

Particularly relevant confirmation comes from a cross-sectional study of 91 obese individuals without diabetes. Participants were divided into three groups based on their degree of insulin resistance. In subjects with moderate insulin resistance, insulin clearance was already reduced, while insulin secretion had not yet increased significantly; in the group with more marked insulin resistance, the lower clearance was also associated with higher secretion. This result confirms the narrative that clearance can change in the early stages of adaptation to insulin resistance. Since the study is observational and cross-sectional, it does not prove that lower clearance necessarily occurs first in every person, nor that it is the cause [1].A prospective cohort added a temporal element. In the PROMISE study, 492 adults at risk for diabetes were evaluated over four visits spanning nine years using an oral glucose tolerance test. Estimates of insulin clearance, derived from the C-peptide to insulin ratio, decreased by 20% overall; lower baseline clearance and its decrease over time were associated with the onset of dysglycemia. This confirms the general direction of the relationship described in the book, linking reduced clearance to subsequent worsening of glycemic control. However, it remains an observational association, and the indices obtained from the oral test are indirect measures, not consecutive clamps [2].Overall, the two independent studies converge with the original research on an essential point: lower insulin clearance is observed in conditions of lower insulin sensitivity and poorer glucose regulation. The confirmation is more robust for the pathophysiological association than for the use of clearance as an individual predictor or as a therapeutic target.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results. However, there is significant evidence of methodological complexity. An analysis based on nine studies, involving 2,067 participants undergoing glucose and insulin infusions, standardized clearance for the level of insulin secretion. In this model, insulin sensitivity was the main determinant of standardized clearance, but type 2 diabetes and higher mean glycemia were positively associated with this index. The authors proposed that this reflects multiple, dysfunctional adaptive processes, rather than a simple linear relationship between diabetes and clearance [3].This apparent contrast does not invalidate the original study, because the measures are not identical: k7 is a parameter of a consecutive clamp model, while clearance standardized for secretion seeks to separate the effect of increased insulin production. The result calls for caution: the direction of the association may depend on the estimation method, the level of secretion, and the metabolic phase considered.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to confirm or define the scope of the book's narrative passage.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Human experimental study with consecutive clamps and mathematical modeling	113 adults: 47 with normal tolerance, 16 with impaired tolerance, 50 with type 2 diabetes	The k7 clearance parameter decreased with worsening glucose tolerance and was associated with higher postprandial glycemia.	direct confirmation	moderate
[1]	Cross-sectional observational	91 obese adults without diabetes	Reduced clearance appeared with insulin resistance; increased secretion emerged primarily in the most insulin-resistant subjects.	direct confirmation	moderate
[2]	Longitudinal observational	492 adults at risk for diabetes, four visits over nine years	Clearance decreased by 20%; lower values and reductions over time were associated with incident dysglycemia.	direct confirmation	moderate
[3]	Physiological analysis with mathematical modeling	Nine studies with glucose and insulin infusions, up to 2,067 participants	The relationship between clearance, secretion, sensitivity, glycemia, and diabetes changes after standardization for insulin secretion.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication clearly supports that a modeling parameter of insulin clearance decreases in groups with progressively worse glucose tolerance and that lower values are associated with higher postprandial glycemia. Independent evidence confirms that reduced clearance accompanies insulin resistance and dysglycemia, even over time. The narrative is moderately supported, but it does not allow us to conclude that the reduction in clearance causes diabetes or that it is a sufficient predictive test in clinical practice.

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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