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Insulin clearance and type 2 diabetes risk in Native Americans

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1. ABSTRACT

The analyzed study evaluated whether lower metabolic insulin clearance—the rate at which the body removes the hormone from the blood—was associated with the future development of type 2 diabetes. It followed 448 Native American adults initially without diabetes for a median of 7.9 years; 146 developed diabetes. At baseline, lower clearance was associated with greater adiposity, higher fasting insulin, greater acute insulin response, and lower insulin action.The research contributes to the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, which suggests that reduced insulin elimination may be an early indicator of metabolic risk rather than just a response to insulin resistance. An independent cohort observed a similar prospective association; another linked increases in alanine aminotransferase to reductions in clearance over time. However, results in a different sample show that the association may attenuate when insulin sensitivity and pancreatic secretion are considered together. The conclusion is therefore cautious: clearance is a relevant factor, but its causal autonomy remains to be defined.

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 whether lower insulin clearance could identify individuals at higher risk of developing type 2 diabetes. Insulin clearance describes how quickly the hormone is removed from circulation: lower clearance can contribute to higher blood insulin concentrations even without a proportionally greater pancreatic secretion.The study is relevant to two passages from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi. In chapter 3, it contributes to the proposal that liver alterations, also indicated by elevated alanine aminotransferase, may be accompanied by reduced insulin extraction. In chapter 14, it primarily supports the passage stating that reduced clearance may have prognostic value for diabetes, even after accounting for other metabolic factors.As a prospective observational study, it can show that clearance measured before diagnosis is associated with the subsequent onset of diabetes. However, it cannot demonstrate on its own that reducing clearance causes diabetes, nor can it establish that hepatic steatosis is the cause of reduced insulin elimination.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

At baseline, 570 Native American adults living in the Southwestern United States without diabetes were characterized. Follow-up data were available for 448 participants for the prospective analysis. The median follow-up was 7.9 years.Body composition was assessed using dual-energy X-ray absorptiometry or hydrodensitometry. Participants underwent a 75 g oral glucose tolerance test, an intravenous glucose tolerance test to estimate the acute insulin response, and a hyperinsulinemic-euglycemic clamp. The clamp is an experimental test in which insulin and glucose are regulated in a controlled manner to measure both insulin action and insulin clearance.Incident diabetes was defined as a fasting glycemia of at least 7.0 mmol/L, a two-hour glycemia of at least 11.1 mmol/L, or a clinical diagnosis. Detailed inclusion and exclusion criteria, the precise enrollment period, dosages, and further statistical procedures are not reported in the available material, which contains only a portion of the abstract.

4. RESULTS

In the group followed over time, 146 of the 448 participants, equal to 32%, were diagnosed with diabetes during the follow-up. This figure indicates a high frequency of new cases in the studied population, but it cannot be automatically applied to populations with different origins, ages, body compositions, or metabolic risks.At baseline, lower insulin metabolic clearance was associated with a higher percentage of body fat, higher fasting insulin concentrations, and a more intense acute insulin response. The reported correlations were inverse for body fat, fasting insulin, and acute insulin response, respectively; conversely, clearance was positively associated with the amount of glucose utilized under insulin stimulation, an indicator of insulin action. In simple terms, those who cleared insulin more slowly also tended to have a less favorable metabolic profile.The available material also reports that the authors used adjusted models to examine the association between clearance and incident diabetes. However, the precise value of the hazard ratio—that is, the ratio of the rate at which diabetes appears in the compared groups—and the relative confidence intervals are not reported in the provided text. The book excerpt summarizes a reduction of approximately 23% in risk for every one-standard-deviation increase in clearance; this value cannot be directly verified in the attached available material.

5. INTERPRETATION

The main implication is that the concentration of insulin in the blood does not depend solely on how much hormone the pancreas produces. It also depends on how effectively the liver, kidneys, and other tissues remove it. Reduced clearance can therefore contribute to hyperinsulinemia, which is the persistent presence of elevated insulin in the blood.The segment documented by the publication subject to the Evidence Review is: lower metabolic insulin clearance higher observed probability of type 2 diabetes in subsequent years. The work also supports a link between reduced clearance and a profile including higher adiposity, higher fasting insulin, and lower insulin action. However, it does not demonstrate the entire sequence proposed in the book—that is, that lower insulin elimination directly causes insulin

resistance, pancreatic beta-cell overload, and diabetes.The reference to alanine aminotransferase, an enzyme that can increase in the presence of liver distress or fat accumulation, should be interpreted with particular caution. An association with this biomarker is biologically consistent with possible liver involvement, but alanine aminotransferase alone does not diagnose steatosis and does not establish a causal relationship.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent prospective confirmation comes from the IRAS Family Study, which followed 1,116 Hispanic and African American adults without diabetes for approximately five years. Metabolic insulin clearance was estimated using a frequently sampled intravenous test. For every one-standard-deviation reduction in clearance, the probability of incident diabetes was approximately doubled after adjusting for demographic variables, lifestyle, adiposity, and insulin secretion: odds ratio 2.01; 95% confidence interval 1.30–3.10. This directly confirms the prognostic part of the book's narrative, while remaining observational data and therefore not causal [1].Regarding the section on the liver, the PROMISE cohort followed 492 adults at risk for diabetes across four assessments over nine years. Clearance, estimated by the C-peptide to insulin ratio during an oral glucose tolerance test, decreased by 20% over the observed period. Higher baseline alanine aminotransferase values, along with greater waist circumference and white blood cell counts, were associated with a reduction in clearance over time. The study does not directly measure steatosis via biopsy or imaging in all participants, but it reinforces the idea that markers consistent with hepatic metabolic alterations are accompanied by a loss of clearance [2].The two cohorts therefore support different parts of the same chain: the first shows that lower clearance statistically precedes more diabetes diagnoses; the second links the worsening of clearance to metabolic factors, including elevated alanine aminotransferase. Neither study demonstrates that intentionally modifying clearance prevents diabetes.

7. CONFLICTING EVIDENCE

A relevant element of caution comes from the MILES study, a cross-sectional analysis of 353 non-Hispanic white and African American adults. In separate models, lower clearance was associated with a higher prevalence of early dysglycemia, i.e., prediabetes or newly identified type 2 diabetes. However, when clearance, insulin sensitivity, and insulin secretion were considered together, clearance did not remain an independent predictor, whereas insulin resistance and lower secretion maintained the association [3].This result does not negate the association observed in the original study, because the population, design, clearance measurement, and outcomes were different. It does, however, show that clearance is closely intertwined with insulin sensitivity and beta-cell function. Consequently, it is not yet possible to universally consider it an autonomous causal factor for diabetes. No directly conflicting evidence sufficiently relevant to the specific association between alanine aminotransferase and longitudinal reduction in clearance has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication that is the subject of the review from the independent research used to confirm or contextualize the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Prospective observational cohort	570 Native American adults without diabetes; 448 followed up	Lower insulin clearance was associated with an unfavorable metabolic profile and a higher subsequent incidence of diabetes.	direct confirmation	moderate
[1]	Prospective observational cohort	1,116 Hispanic and African American adults without diabetes	Lower insulin clearance was associated with higher odds of incident diabetes at five years: OR 2.01 per one standard deviation reduction.	direct confirmation	moderate
[2]	Longitudinal observational cohort	492 adults at risk for diabetes	Clearance decreased by 20% over nine years; higher baseline alanine aminotransferase was associated with a subsequent reduction in clearance.	indirect confirmation	moderate
[3]	Cross-sectional observational study	353 non-Hispanic white and African American adults	Lower clearance was associated with dysglycemia in separate models, but did not remain independent when considering insulin sensitivity and secretion together.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

Reduced insulin clearance is moderately supported as an indicator of an unfavorable metabolic profile and a higher future risk of type 2 diabetes. The consistency across independent cohorts makes the prognostic signal robust, while the link to the liver is biologically plausible but primarily indirect. It has not yet been proven that reduced clearance is an autonomous and universal cause of diabetes, nor that intervening directly in this process prevents the disease.

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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