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ORIGINAL RESEARCH

Impaired insulin clearance as a cause rather than a consequence of insulin resistance - A review of the evidence

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1. ABSTRACT

The analyzed publication examines the hypothesis that reduced insulin clearance—that is, the body's, and especially the liver's, reduced ability to remove the hormone from the blood—may be an initial event in insulin resistance. It does not present a new clinical trial, but integrates previous data from humans and animal models to propose a sequence: reduced insulin elimination, persistent hyperinsulinemia, and subsequent reduction in tissue response to the hormone.The reference in "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns precisely this possible reversal of the traditional paradigm, in which lower clearance was considered merely a compensation for insulin resistance. A prospective cohort study in Native American adults associates lower clearance with a higher future risk of type 2 diabetes; targeted experiments in mice also show a temporal sequence compatible with a causal role. However, an older study in people with already manifest diabetes found higher clearance, indicating that the phenomenon may depend on the stage of the disease. Overall, the narrative is moderately supported, with causality demonstrated primarily in the animal model.

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 is whether reduced insulin clearance might be a cause, rather than just a consequence, of insulin resistance. Insulin clearance refers to the rate at which insulin is removed from the bloodstream following pancreatic secretion; the liver is the primary organ involved in the first pass of the hormone from the portal vein to the general circulation.The publication is relevant to section 3.3 of the book because it addresses the central point of its narrative: reduced hepatic insulin elimination can consistently increase the exposure of muscle, liver, and adipose tissue to the hormone. The authors propose that this chronic hyperinsulinemia may promote a less effective insulin response, with reduced glucose utilization and persistent lipid accumulation.However, this is a hypothesis and interpretive synthesis article, not an original experimental study with a new cohort or a new intervention. It can therefore organize previous results in a biologically plausible way, but it cannot demonstrate on its own that reduced clearance causes insulin resistance in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The analyzed publication does not describe an original experimental protocol, does not enroll participants, and does not assign treatments. The authors discuss previous studies conducted using the hyperinsulinemic-euglycemic clamp, a procedure that allows for the measurement of both insulin sensitivity and the metabolic clearance of the hormone under controlled conditions.The text references observations in non-obese Japanese men, mouse models with *Slc30A8* or CEACAM1 alterations, and genetic data on the heritability of clearance. CEACAM1 is a protein that facilitates the entry of insulin into liver cells and contributes to its removal. However, for most of the cited studies, the available material does not report sample sizes, selection criteria, observation periods, complete quantitative values, or detailed statistical analyses.The structure of the article is therefore argumentative. Its pathophysiological hypothesis is that reduced clearance increases circulating insulin; persistent hyperinsulinemia would primarily reduce signals dependent on the IRS-2 protein, a component of insulin signaling transmission, while leaving certain signals linked to fat synthesis relatively more preserved.

4. RESULTS

The publication does not generate new experimental results. Its main finding is a reinterpretation of the available literature: in metabolically healthy individuals, there may be differences in insulin clearance, and lower clearance may be associated with reduced insulin sensitivity in the muscle. The authors emphasize that this association is compatible with both a compensatory response and the opposite hypothesis, namely that reduced clearance precedes at least part of the insulin resistance.The text proposes a possible mechanism. If the liver removes less insulin, the concentration of the hormone in the blood increases. Prolonged exposure to high concentrations could attenuate some of the effects of insulin, particularly glucose transport in the muscle and the suppression of glucose production by the liver. At the same time, lipid synthesis and storage could remain relatively active. This scenario is defined as selective insulin resistance.The authors also cite mouse models in which reduced CEACAM1 function was accompanied by lower clearance, hyperinsulinemia, and insulin resistance. However, the available material for the analyzed publication does not report absolute values, confidence intervals, probability values, or a quantitative meta-analysis. The proposed conclusion therefore remains a hypothesis supported by heterogeneous data, not definitive clinical proof.

5. INTERPRETATION

In simple terms, the publication suggests that a high blood insulin level should not be automatically interpreted as proof of increased secretion by the pancreas. The circulating concentration actually depends on two processes: how much insulin is produced and how much is cleared. Reduced insulin clearance can increase blood insulin levels even without a proportional increase in pancreatic secretion.The segment of the chain most directly documented by the publication is: reduced insulin clearance persistent hyperinsulinemia possible selective insulin resistance. The hypothesis is biologically consistent with the role of the liver and with experimental models that modify CEACAM1.

However, it does not prove that all people with insulin resistance began the process with reduced clearance, nor that obesity loses its importance as a causal factor.The analyzed publication was therefore included in the book's section to support a shift in perspective: reduced insulin clearance may be an initial pathogenetic element in some cases. Subsequent independent literature allows for an assessment of how well this hypothesis is supported in humans and animal models.

6. INDEPENDENT SUPPORTING EVIDENCE

The most significant confirmation in humans comes from a longitudinal cohort of 570 Native American adults without diabetes at enrollment. Insulin clearance and insulin sensitivity were measured using a hyperinsulinemic-euglycemic clamp. Among the 448 participants followed for a median of 7.9 years, 146 developed diabetes. Higher clearance was associated with a lower probability of developing diabetes: hazard ratio or HR of 0.77 per standard deviation increase in clearance, 95% confidence interval from 0.61 to 0.98; P = 0.03. Therefore, in the opposite direction, lower clearance was associated with a higher future risk of diabetes, even after adjusting for adiposity, insulin secretion, and insulin sensitivity [1]. This study confirms the prognostic shift in the book's narrative, but as it is observational, it does not prove that lower clearance is the cause of the event.A causal pathway was studied in mice with a selective deletion of the *Ceacam1* gene in the liver. Compared to controls, the mutant animals already showed lower clearance and hyperinsulinemia at two months; they subsequently developed hepatic insulin resistance, measured via clamp, and steatohepatitis. Controlled feeding experiments also distinguished the initial phase of lower clearance from the subsequent hyperphagia, i.e., the increase in food intake [2]. This experimental sequence supports the model of reduced clearance hyperinsulinemia insulin resistance, but it remains evidence in mice and not a direct demonstration in humans.The two pieces of evidence are complementary. The human study shows that lower clearance statistically precedes a higher risk of diabetes in a defined population; the mouse model shows that a targeted hepatic modification can precede insulin resistance. Together, they support the plausibility of the direction proposed by the analyzed publication, even without making the mechanism universal.

7. CONFLICTING EVIDENCE

There is directly relevant evidence that calls for caution. In a small cross-sectional study, ten Pima individuals with pre-existing type 2 diabetes had a higher metabolic insulin clearance compared to eight non-diabetic controls with comparable obesity: 436 ± 22 versus 325 ± 24 ml/m²/min, P < 0.005. The extraction of secreted insulin after oral glucose was also higher in the group with diabetes, 88.9 ± 2.5% versus 72.0 ± 2.8%, P < 0.001 [3].This result does not necessarily disprove the possibility that reduced clearance contributes to the early stages in other individuals. The study, in fact, compared subjects with already diagnosed diabetes and a very small group, whereas the more recent cohort evaluated people initially without diabetes and followed the incidence of the disease. However, it shows that clearance does not have a single direction across all clinical stages: in overt diabetes, reduced pancreatic secretion, hepatic changes, and other adaptations can alter the picture.No sufficiently relevant directly conflicting evidence has been identified that experimentally refutes, in humans before the onset of diabetes, the entire proposed sequence; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the hypothesis formulated in the original study from independent confirmations and the evidence that defines its generalizability.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Hypothesis and narrative review article	Previously published human and animal literature	Proposes that reduced clearance may precede hyperinsulinemia and selective insulin resistance.	biologically consistent evidence	preliminary
[1]	Prospective observational	570 non-diabetic Native American adults; 448 followed	Lower clearance was associated with a higher future incidence of type 2 diabetes.	direct confirmation	moderate
[2]	Experimental animal	Male mice with hepatic Ceacam1 deletion and controls	Lower clearance and hyperinsulinemia preceded hepatic insulin resistance.	direct confirmation	moderate
[3]	Cross-sectional observational	10 Pima individuals with type 2 diabetes and 8 controls with comparable obesity	In manifest diabetes, clearance was higher in the diabetes group.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the hypothesis that insulin clearance is an active regulator of hyperinsulinemia rather than a simple elimination mechanism. The narrative is moderately supported by a prospective human cohort and an animal model in which the temporal sequence was experimentally manipulated.However, the evidence does not allow us to conclude that reduced clearance is the initial cause of insulin resistance in all individuals or in every form of type 2 diabetes. Divergent results in manifest diabetes suggest that clearance may change with the stage of the disease. The mechanism remains promising, but requires validation in diverse cohorts and with repeated measurements over time.

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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