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Hyperinsulinemia and hepatic insulin resistance in mice with hepatic Ceacam1 deletion

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1. ABSTRACT

The analyzed study examined male mice with selective deletion of the *Ceacam1* gene in the liver, which is involved in the clearance of insulin from the blood. Researchers first observed reduced hepatic insulin clearance and hyperinsulinemia, and only subsequently hepatic insulin resistance and steatohepatitis. The result supports a timeline in which impaired hormone clearance can precede other metabolic alterations.In section 3.4 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that reduced insulin clearance may be at the beginning of the cascade leading to hyperinsulinemia and, in some contexts, subsequent insulin resistance. Independent studies in humans show that reduced clearance contributes to hyperinsulinemia during mild weight gain, is associated with future metabolic risk, and may worsen with insulin resistance. However, other data indicate that in some people with obesity, increased pancreatic secretion may prevail over reduced clearance. The confirmation is therefore mechanistic and moderate, not a complete causal demonstration in humans.

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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.

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2. ANALYZED STUDY

The research question was whether the loss of CEACAM1 in the liver could impair insulin clearance and, over time, trigger insulin resistance. CEACAM1 is a protein involved in the uptake and degradation of insulin by liver cells. Since the liver is the primary organ responsible for removing insulin immediately after its secretion from the pancreas, a slowdown in this process can increase the amount of the hormone reaching the general circulation.The relevance to the book's section is precise: the publication is not used to demonstrate that every case of human hyperinsulinemia depends on clearance, but rather to experimentally document a possible sequence. In the animal model, the defect in hepatic insulin clearance and hyperinsulinemia were observable before hepatic insulin resistance, visceral obesity, and increased lipolysis—that is, the release of fatty acids from adipose tissue.The study can therefore demonstrate a temporal and causal relationship within a specific genetically modified mouse model. It cannot establish that the same sequence necessarily occurs in humans, nor can it quantify how often reduced clearance is the initial cause of insulin resistance in the general population.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Researchers generated male C57BL/6J mice with liver-specific *Ceacam1* deletion, referred to as AlbCre+Cc1fl/fl, and compared them with littermate controls. The animals were characterized between 2 and 9 months of age.Insulin sensitivity was assessed using the hyperinsulinemic-euglycemic clamp, a technique in which insulin is infused while maintaining stable glycemia: if less glucose is required to maintain stable glycemia, this indicates a reduced response to insulin. Indirect calorimetry was also used to estimate energy expenditure and metabolic activity, along with pair-feeding trials, in which controls receive the same amount of food as the mice with the mutation.The available material consists only of the abstract. The sample size for each group, inclusion and exclusion criteria for the animals, full details of the experimental protocols, individual measurement values, statistical analyses, and P-values are not reported in the available material.

4. RESULTS

At 2 months of age, mice with hepatic CEACAM1 loss showed reduced insulin clearance and hyperinsulinemia. In simple terms, the liver removed the hormone from the blood less effectively, and insulin levels remained elevated in circulation. At this early stage, according to the abstract, visceral obesity, steatosis, increased lipolysis, or systemic insulin resistance were not yet present.Only around 7 months did hepatic insulin resistance, assessed via hyperinsulinemic-euglycemic clamp, and steatohepatitis appear. During the same period, visceral obesity, increased food intake, and elevated leptin levels developed. Leptin is a hormone that helps control hunger; in mutant mice, the hypothalamic response to leptin was attenuated, as assessed by reduced phosphorylation of STAT3, a protein that transmits the leptin signal in nerve cells.The authors also report that hyperinsulinemia was associated with insulin resistance in the hypothalamus, the brain region that regulates hunger and energy expenditure. This alteration, together with the reduced response to leptin, contributed to increased food intake and decreased physical activity. Pair-feeding experiments indicated that hyperphagia subsequently contributed to the systemic insulin resistance observed at 8-9 months, including a reduced response to insulin in white adipose tissue and increased lipolysis.The central finding for the book's section is therefore the temporal direction observed: reduced hepatic insulin clearance and hyperinsulinemia appeared before hepatic insulin resistance and before the increase in lipolysis. Quantitative values for the differences and their relative statistical significance are not reported in the available material.

5. INTERPRETATION

The biological significance is that insulin resistance should not be considered solely as the condition that induces the pancreas to produce more insulin. In this model, a liver that clears less insulin first increases the chronic exposure of tissues to the hormone. Subsequently, a reduced hepatic response to insulin occurs.The segment of the chain documented directly is: loss of CEACAM1 hepatic function reduced hepatic insulin clearance early hyperinsulinemia subsequent hepatic insulin resistance. Pair-feeding experiments

reinforce the interpretation that lipolysis was not the initial event, because the hepatic alteration emerged before the increase in lipolysis.The causal interpretation is strong in the context of the genetic model used, but it does not equate to proof that CEACAM1 is the primary determinant of hyperinsulinemia in all people. The complete and selective deletion of a gene in the liver is an experimental condition much more clear-cut than the metabolic variations usually observed in humans. Furthermore, since the available material only reports the abstract, some details essential for judging the breadth and precision of the effects are not available.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial confirmation suggests that reduced clearance may contribute to hyperinsulinemia from the very early stages of weight gain. In an experimental study conducted on 10 healthy men, an intentional increase of 2 points in body mass index over approximately four and a half months increased basal insulin, C-peptide, and glycemia. The researchers' estimates indicated that reduced clearance contributed more to fasting hyperinsulinemia than increased secretion; after a meal, oral glucose, and intravenous stimulation, the rise in insulin was attributed to lower clearance, while C-peptide and glycemia did not differ. This is human confirmation of the transition from reduced clearance higher circulating insulin, but the sample was very small and the study did not demonstrate that reduced clearance alone caused insulin resistance [1].A second study examined 460 participants in one cohort and 81 in a second cohort that also underwent a hyperinsulinemic-euglycemic clamp. In adults with obesity without diabetes, insulin clearance was reduced in all obese participants and decreased further as insulin resistance increased. In the early stages of metabolic deterioration, insulin secretion appeared substantially unchanged according to the authors. These data are consistent with the book's narrative, as they show that insulin elimination can contribute to hyperinsulinemia without necessarily requiring an initial increase in secretion. However, as this is a cross-sectional observational analysis, the proposed temporality cannot be considered proven [2].A third piece of evidence comes from 1,116 Hispanic and African American adults without diabetes followed for approximately five years. In 71 participants, equal to 6.4%, type 2 diabetes developed. A lower baseline metabolic clearance rate of insulin was associated with a higher probability of incident diabetes, with an odds ratio of 2.01 for every one-standard-deviation reduction in clearance after adjustment for multiple metabolic factors and insulin secretion; the 95% confidence interval was 1.30-3.10 and the P-value was 0.0064. This finding does not demonstrate the hepatic mechanism observed in mice, but it indicates that lower clearance can precede an unfavorable metabolic outcome in humans [3].

7. CONFLICTING EVIDENCE

An analysis conducted on 92 people without diabetes shows that the relative contribution of secretion and clearance changes depending on the context. People with obesity but preserved insulin sensitivity had a greater area under the insulin curve and higher insulin secretion compared to insulin-sensitive overweight individuals, while clearance was similar. A decrease in clearance, however, appeared in the subgroup with obesity and insulin resistance, in which both insulin and secretion were increased and clearance was reduced [4].This result does not negate the experimental sequence observed in mice, but it limits its generalizability: in humans, the hyperinsulinemia associated with obesity does not always stem primarily from reduced clearance. In some individuals, it may be sustained mainly by increased pancreatic secretion, while in others, reduced insulin elimination becomes more relevant when insulin resistance is already present. No further directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the original experimental model from independent verifications in humans and from the evidence that defines the context of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal, genetic intervention	Male mice with hepatic Ceacam1 deletion	Reduced insulin clearance and hyperinsulinemia at 2 months; subsequent hepatic insulin resistance, prior to increased lipolysis.	direct confirmation	moderate
[1]	Experimental human intervention	10 healthy men with intentional weight gain	Reduced clearance contributed to increased insulin, especially after food or glucose stimulation.	direct confirmation	moderate
[2]	Cross-sectional observational	541 adults in two cohorts, including obese participants without diabetes	Clearance was reduced in obesity and decreased further with greater insulin resistance.	indirect confirmation	moderate
[3]	Prospective observational	1,116 Hispanic and African American adults without diabetes	Lower metabolic clearance was associated with a higher probability of incident diabetes at five years.	biologically consistent evidence	moderate
[4]	Cross-sectional observational	92 adults without diabetes, who are overweight or obese	In insulin-sensitive obesity, secretion increased without a reduction in clearance; clearance decreased with insulin resistance.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study convincingly argues, within its mouse model, that a defect in hepatic insulin clearance may precede hyperinsulinemia and subsequent hepatic insulin resistance, without increased lipolysis being the initial event. Independent evidence in humans confirms that clearance significantly contributes to insulin levels and may precede unfavorable metabolic outcomes.The most prudent conclusion is that reduced insulin clearance represents a possible early regulator of hyperinsulinemia in certain contexts, rather than a sole explanation. The relative contribution of clearance and pancreatic secretion changes with obesity, insulin sensitivity, fat distribution, and disease stage. Full causality in humans requires further longitudinal studies with direct and repeated measurements of hepatic clearance.

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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