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ORIGINAL RESEARCH

Impaired insulin clearance as an early regulator of hyperinsulinemia associated with obesity: new insights into the underlying mechanism based on serum bile acid profiles - A review of the evidence

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1. ABSTRACT

The analyzed study evaluated whether hyperinsulinemia, i.e., an elevated concentration of insulin in the blood, in obesity depends primarily on increased pancreatic secretion or reduced hormone clearance. In two cohorts totaling 541 participants, the authors observed reduced insulin clearance in all subjects with obesity. At early levels of insulin resistance, insulin secretion was not found to be increased.This finding contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which states that the increase in circulating insulin does not necessarily require greater pancreatic production but may depend on reduced clearance. Independent human studies confirm that reduced clearance can precede a detectable increase in secretion in some subjects with obesity and insulin resistance. Other studies, however, show that in insulin-sensitive obesity, increased secretion may play a prevalent role. The narrative is therefore moderately supported, but does not demonstrate a universal causal sequence.

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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 whether the hyperinsulinemia associated with obesity stems primarily from increased insulin production by pancreatic beta cells or from reduced insulin clearance—that is, the slower rate at which the hormone is removed from the blood. The authors also explored the association between clearance and circulating bile acids, molecules produced by the liver that participate in digestion and also perform metabolic signaling functions.The publication is relevant to section 3.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it directly examines the two determinants of insulinemia: secretion and clearance. The specific point supported is that, in the early stages of insulin resistance in obesity without diabetes, an increase in blood insulin can occur even without a measurable increase in pancreatic secretion, in the presence of reduced clearance.The study can describe differences and associations between obesity, insulin resistance, clearance, secretion, and bile acids. However, it cannot establish with certainty that reduced clearance is the initial cause of hyperinsulinemia in every person with obesity, nor can it demonstrate that the identified bile acids directly modify clearance in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract. The study used two cohorts. In the first, 460 participants were recruited, and insulin secretion, insulin sensitivity, and endogenous insulin clearance were evaluated using an oral glucose tolerance test. This test measures the body's response after glucose intake.In the second cohort, consisting of 81 participants, the authors performed an intravenous glucose tolerance test and a hyperinsulinemic-euglycemic clamp. The clamp is an experimental procedure that keeps glycemia controlled while insulin is administered, allowing for the estimation of insulin sensitivity and the removal of the hormone from the blood. In this cohort, the secretion and clearance of the insulin produced by the body, the clearance of infused insulin, and insulin sensitivity were estimated.Participants with obesity without diabetes were then divided based on the severity of insulin resistance: into ten ordered groups in the first cohort and three groups in the second. In the second cohort, 40 serum bile acids were measured to examine their association with insulin clearance. Detailed inclusion and exclusion criteria, age, sex distribution, recruitment period, absolute values of metabolic parameters, and the complete statistical plan are not reported in the available material.

4. RESULTS

The main finding is that all participants with obesity exhibited impaired insulin clearance. In simple terms, their bodies cleared insulin from the blood less effectively. In subjects with obesity without diabetes, clearance worsened further as insulin resistance increased.The most relevant data for the book's section concerns the initial phase. In the first cohort, insulin secretion did not change between the first and third of the ten groups ordered by insulin resistance. In the second cohort, no differences in secretion were observed between the three groups. Therefore, in the least compromised groups examined, the increase in circulating insulin was consistent with a reduced elimination of the hormone without a parallel detectable increase in secretion.The authors also identified associations between certain bile acids and clearance. After adjusting for the confounding factors considered, higher concentrations of conjugated bile acids, particularly glycodeoxycholic acid and taurodeoxycholic acid, were associated with lower insulin clearance: $b = -0.335$, $P = 0.004$ and $b = -0.333$, $P = 0.003$, respectively. A higher ratio of unconjugated to conjugated bile acids was instead associated with greater clearance, $b = 0.335$, $P = 0.002$. The b coefficient indicates the direction of the association in the statistical model; these data do not prove that bile acids are the cause of the variations in clearance.The abstract does not report the absolute values of clearance, insulin, or secretion in the individual groups, nor the exact sizes of the subgroups. Therefore, no further quantitative differences, confidence intervals, or detailed analyses by sex, age, and body composition are available in the provided material.

5. INTERPRETATION

To maintain stable glycemia, the body regulates both how much insulin is produced and how quickly it is removed. If the liver and other tissues clear less

insulin, a greater amount of the hormone remains in circulation even if the pancreas does not increase its production. This is the essential physiological meaning of the observed result.The publication subject to the Evidence Review documents, above all, the segment: obesity with initial worsening of insulin sensitivity reduction in insulin clearance greater exposure of the blood to insulin. The comparison between groups suggests that, in the early levels of insulin resistance studied, the reduction in clearance may be detectable before an increase in secretion. This corresponds to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, but it does not prove that this temporal order occurs in every individual.The definition of "initial regulator" requires particular caution. The cohorts were analyzed at a specific moment in time and do not follow the same people over time from insulin normosensitivity to the development of hyperinsulinemia. Furthermore, the association with bile acids is interesting from a biological point of view, but it remains observational: it could reflect other hepatic, intestinal, or metabolic changes that simultaneously influence bile acids and clearance.

6. INDEPENDENT CONFIRMING EVIDENCE

A first independent study compared 23 people with obesity and 45 people without obesity during normal daily activities, using integrated insulin and C-peptide concentrations over 24 hours. C-peptide is secreted along with insulin but is eliminated through different mechanisms; comparing it with insulin allows for an indirect estimate of the relative weight of secretion and clearance. In people with obesity, integrated insulin was 69% higher, while C-peptide increased by 13%. The C-peptide/insulin ratio decreased by 33%, a result interpreted as a reduction in clearance; the authors estimated that approximately 75% of the observed hyperinsulinemia was attributable to reduced insulin elimination [1]. This study directly confirms the concept that the hyperinsulinemia of obesity does not automatically equate to hypersecretion. The main limitation is the observational design and the use of an indirect estimate of hepatic clearance.Evidence closer to the idea of an early event comes from an experimental study conducted on ten healthy men who underwent an intentional increase of two points in their body mass index. After weight gain, fasting insulin increased; the authors calculated that reduced clearance contributed more than secretion to this increase. After a meal, oral glucose, or intravenous stimulation, insulin increased, while C-peptide and secretion did not change significantly; the increase in insulin was therefore attributed to the reduction in clearance [2]. The prospective nature, with measurements taken before and after weight gain, makes this evidence particularly relevant to the book's narrative. However, the sample was very small, exclusively male, and does not allow for broad generalizations.A third study analyzed 91 people with obesity without diabetes, all with a body mass index of at least 30 kg/m², dividing them into three groups with progressively lower insulin sensitivity. In the intermediate group, insulin clearance decreased compared to the most sensitive group, while secretion showed no significant variation. In the group with the highest insulin resistance, clearance decreased and secretion also increased. During the insulin suppression test, the median clearance decreased progressively from 0.48 to 0.43 and to 0.34 in the three groups [3]. This sequence is independent of the original study and directly confirms the finding that a reduction in clearance can be the first measurable response to worsening insulin sensitivity. It remains a cross-sectional study, however, so the temporal order is inferred from the comparison between groups and not observed in the individual participant.

7. CONFLICTING EVIDENCE

A partially conflicting result comes from a study on 92 adults without diabetes that distinguished between insulin-sensitive overweight individuals, insulin-sensitive individuals with obesity, and insulin-resistant individuals with obesity. Compared to the insulin-sensitive overweight group, the group with obesity but preserved insulin sensitivity showed a higher concentration of insulin and greater secretion during graded glucose infusion, with no differences in clearance. Conversely, clearance decreased in the group with obesity and insulin resistance, alongside higher secretion [4].This evidence does not deny that reduced clearance contributes to hyperinsulinemia in obesity with insulin resistance. However, it reduces the generalizability of the idea that clearance is always the primary or main determinant: in insulin-sensitive

obesity, increased secretion may be more important. Differences between studies may depend on participant selection, the severity of insulin resistance, estimation methods, and the fact that obesity and insulin resistance do not necessarily progress in the same way in all individuals.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication covered in the review from independent research that confirms or defines the scope of the book's passage.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Observational with metabolic tests	460 participants in the first cohort and 81 in the second	In obesity, clearance was reduced; at initial levels of insulin resistance, secretion did not differ.	direct confirmation	moderate
[1]	Physiological observational	23 people with obesity and 45 without obesity	Integrated hyperinsulinemia in people with obesity was primarily attributed to reduced insulin clearance.	direct confirmation	moderate
[2]	Prospective experimental	10 healthy men subjected to weight gain	After weight gain, the increase in stimulated insulin was attributed to reduced clearance rather than secretion.	direct confirmation	moderate
[3]	Observational with metabolic tests	91 people with obesity without diabetes	With intermediate insulin resistance, clearance decreased without a significant increase in secretion.	direct confirmation	moderate
[4]	Observational with metabolic tests	92 adults without diabetes, stratified by obesity and insulin resistance	In insulin-sensitive obesity, secretion increased without a reduction in clearance.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed consistently supports the idea that, in obesity without diabetes, a decrease in insulin clearance can contribute to hyperinsulinemia before an increase in pancreatic secretion is observable. Independent evidence confirms this pattern in some contexts, including the initial worsening of insulin sensitivity. However, the effect is not universal: in obesity with preserved insulin sensitivity, increased secretion may be the prevailing determinant. The initial role of clearance is therefore moderately supported, while causality, hepatic mechanisms, and the possible contribution of bile acids require further longitudinal and experimental validation.

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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