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Hyperinsulinemia and insulin resistance in the early stages of weight gain

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1. ABSTRACT

The original study examined whether a small weight gain, still within body mass index values considered normal, could alter insulin metabolism. Ten healthy men intentionally increased their body mass index by two points over approximately four and a half months. After the weight gain, blood insulin and insulin resistance had increased. Analyses based on C-peptide indicated that lower insulin clearance—that is, a lower rate of hormone elimination from circulation—contributed more than pancreatic secretion to basal hyperinsulinemia and fully explained the increase in insulin following glucose stimulation.The research contributes to the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, according to which a reduction in clearance can appear early during the increase in adipose mass. Independent studies confirm that clearance significantly influences insulinemia and that, in obesity, it can decrease before evident increases in secretion. However, other data show that the relative weight of secretion and clearance varies according to obesity, insulin sensitivity, and glycemic status. The most prudent conclusion is that clearance is an important, but not unique, determinant of early hyperinsulinemia.

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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 insulin resistance and hyperinsulinemia can appear even during modest weight gain, before the onset of obesity. The hypothesis was that the increase in circulating insulin did not necessarily depend solely on the pancreas, but also on a reduction in insulin clearance, meaning a decrease in the removal of the hormone from the blood.This issue is relevant because insulin levels in the blood reflect a balance: on one hand, the pancreas secretes it, and on the other, the liver, kidneys, and other tissues remove it. For this reason, a high insulin value does not automatically identify increased pancreatic production. In section 3.4 and section 14.7 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study is relevant to the passage stating that reduced clearance can be an early metabolic adaptation during weight gain and contribute to hyperinsulinemia alongside the onset of insulin resistance.The experimental design allows for the observation of changes that occurred in the same participants after the programmed weight gain. However, it does not allow for determining whether the reduction in clearance is the initial cause of insulin resistance, nor does it allow for extending the results with certainty to women, elderly individuals, subjects who are overweight or obese, or people with diabetes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study involved 10 healthy men. Participants intentionally increased their body mass index, or BMI (the ratio of weight to height), by two points: from 21.8 to 23.8 kg/m² over approximately four and a half months. The final BMI remained within the range commonly classified as normal weight.Before and after the weight gain, the authors measured glucose, insulin, and C-peptide. C-peptide is a substance released along with insulin by the pancreas and helps estimate how much insulin is actually secreted, because it is cleared differently than insulin. The assessments were performed after a meal, after an oral glucose tolerance test of 75 grams of glucose, and during a two-level hyperglycemic clamp. The hyperglycemic clamp is a test in which glycemia is artificially maintained at a predetermined level to observe the insulin response and the amount of glucose required.The authors also calculated insulin secretion and insulin clearance based on insulin and C-peptide concentrations. Detailed inclusion and exclusion criteria, participant age, body composition, practical methods of weight gain, complete statistical analyses, dispersion values, and P-values are not reported in the available material, which consists only of the abstract.

4. RESULTS

Following weight gain, baseline concentrations of insulin, C-peptide, and glucose were significantly higher. In simple terms, even a modest increase in weight was associated with a greater presence of insulin in the blood while fasting. The authors' calculations indicated that, for basal hyperinsulinemia, the reduction in clearance contributed more than the increase in secretion.After a meal, after an oral glucose load, and during both phases of the hyperglycemic clamp, insulin concentrations were significantly higher compared to the initial assessment. Conversely, C-peptide and glucose did not differ between before and after weight gain in the stimulation tests. Since C-peptide is used as an indicator of pancreatic secretion, the authors interpreted this combination as evidence that the increase in stimulated insulin resulted entirely from reduced clearance and not from increased secretion.Insulin sensitivity decreased. When glucose was maintained at 1.38 mmol/L above baseline, the amount of intravenous glucose required was identical before and after weight gain; when the increase was 2.75 mmol/L, it was significantly lower after weight gain. A smaller amount of glucose needed to maintain the established level indicates that the body was responding less effectively to insulin. The abstract does not report the full numerical values or the exact extent of the reduction in sensitivity.

5. INTERPRETATION

The main significance is that the hyperinsulinemia observed after a slight weight gain was not explained solely by a more active pancreas. Insulin could remain in the blood longer because it was cleared more slowly. This is the segment of the chain described in the book that the study directly documents: modest weight gain reduced insulin clearance increased circulating insulin.The liver plays a central role in

clearance because it intercepts a significant portion of the insulin just secreted by the pancreas. However, the study estimated clearance using calculations based on insulin and C-peptide; it did not directly measure first-pass hepatic elimination. Furthermore, the sample was very small and composed exclusively of healthy men. The results therefore support a physiological mechanism that is plausible and observed in the short term, but they do not prove that lower clearance always precedes higher secretion or that it alone triggers type 2 diabetes.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation that fasting insulin is not a simple indicator of insulin resistance comes from a study of 470 Mexican-American adults without overt diabetes. Insulin sensitivity and insulin metabolic clearance were measured using a hyperinsulinemic-euglycemic clamp, a test that maintains normal glycemia while insulin is infused. In multivariate analysis, clearance was independently associated with fasting insulin along with insulin sensitivity, BMI, waist circumference, and glycemia. The authors concluded that basal insulinemia reflects different physiological processes and cannot be interpreted as a measure of insulin resistance alone [1]. This study does not follow individuals during weight gain, but it directly confirms the passage in the book regarding the autonomous contribution of clearance.A second study examined two independent cohorts of young adults: 460 participants evaluated with an oral glucose tolerance test and 81 who also underwent intravenous tests and a hyperinsulinemic-euglycemic clamp. In subjects with obesity, endogenous insulin clearance was reduced compared to lean controls. In the early stages of metabolic impairment, secretion did not increase correspondingly; the authors therefore proposed that reduced clearance may contribute early on to the hyperinsulinemia associated with obesity [2]. This is a cross-sectional observation, so it does not prove the individual temporal sequence, but it reinforces the biological consistency with the original study.A controlled experiment in healthy subjects with normal glucose tolerance added a piece to the possible metabolic chain. After 72 hours of experimentally maintained mild hyperglycemia, approximately 50 mg/dL above usual values, insulin metabolic clearance was markedly reduced and insulin sensitivity decreased. The increase in circulating insulin depended on a small, non-significant variation in secretion and a larger reduction in clearance [3]. This research does not study weight gain, but it shows in humans that an early metabolic perturbation can cause reduced insulin elimination, hyperinsulinemia, and insulin resistance to coexist.

7. CONFLICTING EVIDENCE

No directly conflicting evidence has been identified that is sufficiently relevant to refute the specific result of the original study in healthy men undergoing modest weight gain. However, there is data that warrants caution when generalizing the role of clearance to all stages of obesity and diabetes.In a metabolic study of 106 lean or obese individuals, distributed across different levels of glycemic control, basal clearance was approximately 20-30% lower in the obesity groups compared to the lean group. However, the authors estimated that about one-third of the higher basal hyperinsulinemia was attributable to lower clearance and about two-thirds to higher secretion. After glucose intake, clearance also depended on the amount of insulin secreted and was relatively higher in participants with type 2 diabetes, in whom postprandial secretion was reduced [4]. These results do not negate the findings of the original study, but they show that the relative contribution of secretion and clearance changes with the metabolic context, the stage of the disease, and the type of stimulus studied.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from the independent publications used to verify the narrative passage of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Prospective experimental before-after	10 healthy men; BMI from 21.8 to 23.8 kg/m²	After weight gain, insulin and insulin resistance increased; reduced clearance primarily explained stimulated hyperinsulinemia.	direct confirmation	preliminary
[1]	Cross-sectional physiological observational	470 Mexican-American adults without overt diabetes	Insulin clearance was an independent determinant of fasting insulin.	direct confirmation	moderate
[2]	Cross-sectional physiological observational	460 participants in one cohort and 81 in a second metabolic cohort	In obese subjects, clearance was reduced and could precede a detectable increase in secretion.	direct confirmation	moderate
[3]	Controlled experimental	Healthy adults with normal glucose tolerance	Seventy-two hours of mild hyperglycemia reduced clearance and insulin sensitivity, increasing circulating insulin.	indirect confirmation	moderate
[4]	Cross-sectional metabolic study	106 lean or obese adults with varying glycemic status	In obesity, basal clearance decreased, but increased secretion contributed more than clearance to basal hyperinsulinemia.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed shows that, in ten healthy men, a modest weight gain was accompanied by higher circulating insulin and lower insulin sensitivity. The available analyses suggest that the reduction in clearance played a predominant role, especially following glucose stimulation. The narrative passage in the book is moderately supported by independent evidence in humans: clearance is a relevant determinant of hyperinsulinemia, but it does not operate in isolation. As obesity and glycemic alterations progress, the contribution of pancreatic secretion may increase or become predominant.

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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