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ORIGINAL RESEARCH

Fasting insulin reflects heterogeneous physiological processes: the role of insulin clearance - A review of the evidence

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study evaluated which factors contribute to fasting insulin levels in 470 Hispanic-American adults. Through hyperinsulinemic-euglycemic clamps, oral glucose tolerance tests, and multivariate analyses, metabolic insulin clearance was found to be the factor most strongly associated, in an inverse manner, with basal insulinemia. Lower insulin sensitivity, higher body mass index, greater waist circumference, and higher fasting glycemia also contributed independently.The research is relevant to sections 3.4 and 14.7 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi because it documents that a high blood insulin value does not automatically identify increased pancreatic secretion or insulin resistance alone. Independent evidence confirms that secretion, clearance, and insulin sensitivity interact; however, experimental and clinical studies also show that the relative weight of each process changes according to the metabolic context and the time of day. The most prudent conclusion is that fasting insulin is a composite indicator that should not be interpreted in isolation.

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2. ANALYZED STUDY

The research question was only apparently simple: when fasting morning insulin levels are high, which process matters most? The hypothesis was that the result did not depend exclusively on insulin resistance—that is, the reduced response of muscles, liver, and adipose tissue to the hormone—but rather on a combination of pancreatic production, insulin clearance, and body characteristics.This question is central to the sections of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi dedicated to insulin clearance. Clearance is the rate at which the body removes insulin from the blood; the liver plays a major role in this task. If clearance decreases, the same amount of secreted insulin can remain in circulation longer and produce a higher blood value.The study can therefore document which variables were independently associated with fasting insulin in the examined population. However, it cannot establish whether reduced clearance causes insulin resistance over time, nor can it automatically extend the results to all populations, people with diabetes, or the insulin response after meals.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication analyzed 470 Hispanic-American subjects. The study design was observational, with in-depth physiological measurements taken during a single evaluation period. Only the abstract is available; inclusion and exclusion criteria, recruitment period, distribution by sex and age, and detailed clinical characteristics are not reported in the available material.Insulin sensitivity was measured using the hyperinsulinemic-euglycemic clamp, an experimental procedure in which insulin is administered while blood glucose is kept stable; the amount of glucose required to maintain this balance allows for the estimation of tissue response to insulin. From the same examination, the metabolic clearance rate of insulin, referred to by the authors as MCRI, was derived. Early insulin secretion was estimated using the insulinogenic index at 30 minutes during an oral glucose tolerance test.The authors first evaluated associations one variable at a time and then applied multivariate models using generalized estimating equations. This approach allows for verifying whether a factor remains associated with fasting insulin even when simultaneously considering the other factors included in the model. Full details on covariates, the management of missing data, and sensitivity analyses are not reported in the available material.

4. RESULTS

The main finding is that fasting insulin did not follow a single mechanism. In the multivariate model, lower insulin metabolic clearance and lower insulin sensitivity were associated with higher fasting insulin concentrations. A higher body mass index, a larger waist circumference, and higher baseline glycemia were also associated with higher insulin levels.Among the variables considered, clearance showed the strongest inverse standardized association: coefficient −0.35, with $P < 0.0001$. Simply put, as the ability to clear insulin decreased, the fasting value tended to increase. This was followed by insulin sensitivity, which was also inversely associated with fasting insulin, with a coefficient of −0.24 and $P < 0.0001$; body mass index with a coefficient of 0.20 and $P = 0.0011$; waist circumference with a coefficient of 0.16 and $P = 0.021$; and fasting glycemia with a coefficient of 0.11 and $P = 0.014$.The standardized coefficient allows for comparing the relative strength of associations within the same model, but it does not prove a cause-and-effect relationship. The abstract does not report the total variance explained by the model. For this reason, the statement in the book's paragraph that the parameters would explain approximately 52% of the variability cannot be verified in the material available for this Evidence Review.The insulinogenic index, used as an estimate of early insulin secretion, does not appear among the variables reported as independently associated in the final model of the abstract. This does not mean that secretion is irrelevant to insulinemia: it only means that, with the variables and model described in the available material, the authors highlighted primarily the contribution of clearance, sensitivity, adiposity, and baseline glycemia.

5. INTERPRETATION

For the reader, the message is that insulin in the blood is the result of a balance. The pancreas secretes it, while the liver and other tissues remove it. A high value can therefore arise from an increased release of

the hormone into circulation, a reduced elimination, or both phenomena.The segment of the narrative directly documented by the analyzed study is: reduced metabolic insulin clearance is independently associated with higher fasting hyperinsulinemia, and this association was quantitatively stronger than that with insulin sensitivity in the examined sample. This supports the recommendation not to automatically use fasting insulin as a measure of insulin resistance alone.However, the data does not allow us to conclude that reduced clearance is always the primary determinant of hyperinsulinemia, nor that it is necessarily the first biological event in the development of type 2 diabetes. The causal direction can be bidirectional: insulin resistance, the amount of insulin secreted, and clearance can influence each other. Furthermore, the associations observed in Hispanic-American adults are not equivalent to evidence valid for every age group, geographic origin, or clinical condition.

6. INDEPENDENT SUPPORTING EVIDENCE

Extensive validation comes from an analysis based on nine independent physiological studies, totaling 2,067 participants. The authors mathematically standardized clearance relative to the insulin secretion rate to separate, as much as possible, the reduced elimination of the hormone from the effect of increased production. In the 1,410 participants with data from both clamp studies and oral glucose tolerance tests, insulin sensitivity proved to be the strongest determinant of standardized clearance: its contribution was approximately four times that of the hypersecretion associated with insulin resistance. The study therefore supports the passage in the book stating that clearance and sensitivity are distinct but linked processes, and that interpreting circulating insulin levels alone is insufficient. The main limitation is the use of modeling and the integration of different protocols, rather than a direct measurement of clearance in every participant [1].A controlled experiment in ten healthy men then showed that an intentional weight gain of two body mass index points, from 21.8 to 23.8 kg/m² over approximately four and a half months, was accompanied by an increase in basal insulin, C-peptide, and glucose. The authors' calculations indicated that, in the basal state, the reduction in clearance contributed more to hyperinsulinemia than secretion did. After a meal, oral glucose, or intravenous stimulation, the increase in insulin was attributed to lower clearance, because C-peptide and glucose did not differ significantly. This experimentally confirms that a change in hormone removal can increase measured insulin without a corresponding increase in stimulated secretion. The very small sample size, consisting only of healthy men, limits generalizability [2].Further evidence that clearance can vary greatly between individuals came from twelve healthy young dogs studied with paired infusions into the portal vein and a peripheral vein. First-pass hepatic extraction, i.e., the portion of insulin removed by the liver during the first transit, varied from 22.4% to 77.2%, with a mean of 50.4%. Greater hepatic extraction was associated with higher insulin sensitivity and lower fasting insulin; the correlation between extraction and fasting insulin was inverse, with a Spearman coefficient of –0.64. The result is biologically consistent with the book's narrative, but it is an animal model and does not demonstrate the extent of variability in humans [3].

7. CONFLICTING EVIDENCE

Evidence does not indicate that reduced clearance always explains hyperinsulinemia in the same way. In a clinical study of 60 adults, divided into 14 lean subjects, 24 obese subjects with normal hepatic triglyceride content, and 22 obese subjects with hepatic steatosis and prediabetes, the response after 75 g of glucose was evaluated using clamps, isotopic tracers, and C-peptide modeling. The fractional rate of insulin extracted by the liver decreased progressively from the lean group to the obese groups, but the total amount of insulin removed by the liver per unit of time increased in the obese groups compared to the lean group.The authors concluded that post-glucose hyperinsulinemia in the obese groups depended primarily on increased insulin secretion, not on a decrease in total hepatic or extrahepatic extraction. However, the liver showed a saturable extraction capacity: when insulin delivery increased significantly, total extraction tended to plateau. This finding does not deny that clearance influences circulating insulin; rather, it clarifies that one must distinguish between the extracted fraction and the absolute amount removed, and separate fasting from the postprandial phase [4].This evidence is directly relevant to the

book's narrative because it defines the limit of the simplified formula "high insulin equals low clearance." The relative contribution of hormone secretion and removal changes with adiposity, glucose load, and the clearance parameter considered. No further directly contradictory evidence of sufficient relevance was identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the analyzed study from independent publications and summarizes the level at which each piece of evidence contributes to the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Physiological observational with multivariate analysis	470 Hispanic-American adults	Lower metabolic clearance independently associated with higher fasting insulin; strongest standardized association among reported variables.	direct confirmation	moderate
[1]	Multi-cohort physiological analysis with modeling	Nine studies with glucose and insulin infusions; up to 2,067 participants	Insulin sensitivity was the primary determinant of standardized clearance; clearance decreased with insulin resistance and beta-cell dysfunction.	direct confirmation	moderate
[2]	Before-after experimental study	10 healthy men undergoing controlled weight gain	After weight gain, lower clearance contributed more than secretion to basal hyperinsulinemia and explained the stimulated insulin increase.	direct confirmation	moderate
[3]	Animal experimental study	12 healthy young dogs	First-pass hepatic extraction varied widely and was associated with lower fasting insulin when higher.	biologically consistent evidence	preliminary

[4]	Cross-sectional physiological clinical study	60 lean, obese, and obese adults with steatosis and prediabetes	After glucose, hyperinsulinemia was primarily attributed to increased secretion; total extraction did not decrease, although fractional extraction was reduced.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study clearly supports the fact that fasting insulin is a physiologically composite indicator. In the examined sample, lower metabolic clearance was associated with higher insulin levels, independently of insulin sensitivity, adiposity, and fasting glycemia. This makes it inappropriate to interpret a single insulin value as an exclusive measure of pancreatic secretion or insulin resistance.Independent evidence moderately confirms this interpretation and shows that clearance can change even in the early stages of weight gain. However, the contribution of secretion and clearance varies according to the population, metabolic state, and time of day. The clinical use of fasting insulin therefore requires context and cannot replace a comprehensive metabolic assessment.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **New Insights on the Interactions Between Insulin Clearance and the Main Glucose Homeostasis Mechanisms**
Bizzotto et al., 2021
Diabetes Care
DOI: https://doi.org/10.2337/dc21-0545

[2] **Development of hyperinsulinemia and insulin resistance during the early stage of weight gain**
Erdmann et al., 2008
American Journal of Physiology-Endocrinology and Metabolism
DOI: https://doi.org/10.1152/ajpendo.00560.2007

[3] **Variability of Directly Measured First-Pass Hepatic Insulin Extraction and Its Association With Insulin Sensitivity and Plasma Insulin**
Asare-Bediako et al., 2018
Diabetes
DOI: https://doi.org/10.2337/db17-1520

[4] **Influence of adiposity, insulin resistance, and intrahepatic triglyceride content on insulin kinetics**
Smith et al., 2020
Journal of Clinical Investigation
DOI: https://doi.org/10.1172/JCI136756