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Reduction of insulin clearance during hyperglycemic clamp. Dose-response study in healthy individuals - Evidence review

Dott. A. Colonnese[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study examined eight healthy individuals subjected to three controlled levels of glycemia on different occasions. The goal was to distinguish how much insulin was produced by the pancreas from how much was cleared by the body. At the highest glycemia level, equal to 300 mg/dl, the increase in blood insulin was greater than the increase in estimated insulin secretion; this result is consistent with a reduction in insulin clearance.In paragraph 3.3, “Insulin clearance,” of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that blood insulin concentration depends on both pancreatic secretion and the elimination of the hormone, primarily hepatic. Independent studies confirm that the liver extracts a significant portion of insulin during the first pass and that this extraction can change during metabolic stimuli. However, there are inconsistent results: the effect of glycemia on clearance depends on the glucose level, the duration of exposure, the route by which insulin reaches the liver, and the measurement method. The most prudent conclusion is that clearance is not a fixed parameter, and it is not possible to attribute every observed variation to glucose alone.

ONLINE ARTICLE

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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, in people without diabetes, a progressive and controlled increase in glycemia would only modify insulin secretion by pancreatic beta cells or also its clearance, i.e., the rate at which the hormone is removed from the blood. This is an important distinction: a high concentration of insulin in the blood can depend on increased production, decreased elimination, or both components.The relevance to paragraph 3.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is therefore specific. The research shows that, during strong glucose stimulation, the ratio between secreted insulin and insulin present in peripheral circulation changes in a direction compatible with reduced endogenous insulin clearance. It does not directly measure the amount eliminated by the liver via hepatic catheterization, nor does it prove that every condition of hyperglycemia reduces clearance. Instead, it documents a segment of the chain: greater glucose stimulation, greater insulin secretion, and, at the highest level of glycemia studied, lower relative insulin elimination.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study involved eight healthy subjects. Each participant underwent a hyperglycemic clamp on three separate occasions, a technique in which glucose is infused and regulated to maintain glycemia at a predetermined value. The programmed levels were 120, 225, and 300 mg/dl. Each trial included a one-hour baseline period and three hours of glycemia maintained at the assigned level.Insulin secretion was not inferred solely from circulating insulin. The authors measured C-peptide, a molecule released by the pancreas along with insulin but cleared differently, and applied a two-compartment mathematical model. Individual C-peptide parameters were derived following an intravenous bolus injection of biosynthetic human C-peptide. This approach allows for the estimation of the insulin secretion rate and its comparison with the insulin concentration in peripheral blood.The available material consists only of the abstract. The provided material does not report age, sex, body mass index, detailed inclusion and exclusion criteria, the order of the three clamps, randomization methods, analytical characteristics of the assays, or further statistical details.

4. RESULTS

At the 300 mg/dl level, insulin secretion at the end of the clamp increased up to 9.9 ± 0.7 times the baseline value. In the same interval, the peripheral insulin concentration increased more, reaching 15.4 ± 1.2 times the baseline. The difference between these relative increases was statistically significant (P = 0.002). Simply put, more insulin accumulated in the peripheral blood than would be expected based on the increase in secretion alone; the authors interpreted this discrepancy as an indication of a reduction in the clearance of the insulin produced by the body.At 225 mg/dl, the same numerical trend emerged, but without statistical significance. Circulating insulin increased by 9.9 ± 1.5 times compared to baseline, and estimated secretion by 8.1 ± 0.5 times; P = 0.17. This means that the data do not allow us to rule out that the observed difference is due to the variability of the small sample size.At 120 mg/dl, considered by the authors to be a moderate stimulus, insulin secretion and concentration increased similarly: 2.7 ± 0.2 and 2.4 ± 0.2 times the baseline, respectively, with P = 0.26. At this level, no reduction in endogenous insulin clearance was detected. The key finding is therefore a response dependent on the intensity of the stimulus: the inferred reduction in clearance appeared clearly only at the highest glycemic level examined.

5. INTERPRETATION

For the reader, the main takeaway is that the blood insulin value cannot be interpreted as a direct measure of pancreatic activity alone. If the body removes insulin more slowly, the same secreted amount can lead to higher peripheral concentrations. The analyzed study therefore supports the passage in the book stating that pancreatic secretion and hormone elimination work together to determine how much insulin reaches the muscles, adipose tissue, and other organs.The technical data supporting this interpretation is the comparison between the secretion rate estimated by C-peptide and peripheral insulin. However, the clearance evaluated is an endogenous clearance inferred from the model; it is not equivalent to a direct and selective measurement of first-pass

hepatic extraction. Since insulin is also eliminated by other areas, including the kidneys, the result alone does not quantify how much of the change depends on the liver.The publication does not prove that a reduction in clearance causes diabetes, insulin resistance, or chronic hyperinsulinemia. It demonstrates, in an acute experiment involving eight healthy individuals, that glycemia maintained at 300 mg/dl for three hours is associated with a greater increase in peripheral insulin compared to the increase in estimated secretion. The documented sequence is therefore: strong glucose stimulus increased secretion relative reduction in insulin elimination greater peripheral availability of the hormone.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the liver's regulatory role comes from a study in healthy individuals that estimated hepatic insulin extraction following stimuli capable of increasing endogenous secretion. With oral glucose doses of 10, 25, and 100 g, the hepatic extraction fraction decreased from 67% to 53% and then to 42%, as the liver's exposure to insulin increased. Arginine and a standard meal also produced intermediate values. This study supports the book's premise that the liver does not remove a fixed amount of the hormone and modulates its elimination during an increase in secretion. The estimation model, however, does not completely separate the effects of glucose from those of increased hepatic insulin exposure [1].A second, more direct but very small study obtained simultaneous samples from the hepatic vein and an arterialized vein in five healthy individuals. It found that approximately 80% of insulin was extracted during the first pass through the liver. During a glucose infusion, the fractional extraction rate remained stable, while the absolute amount of insulin cleared by the liver increased; the mass of secretory pulses predicted hepatic clearance with a positive correlation ($r = 0.81$; $P = 0.0043$). This directly confirms the book's assertion that the first hepatic pass regulates how much insulin reaches the systemic circulation and completes the chain by showing that the pancreas and liver respond in a coordinated manner [2].The two studies converge on an essential point: peripheral insulin reflects both pancreatic production and extraction, especially hepatic. However, they are not identical in their quantitative results because the protocols differ. The first study evaluated the effect of secretory stimuli of different magnitudes; the second examined a slight glycemic elevation with direct hepatic sampling. For this reason, the confirmation concerns the dynamic nature of clearance, not a single rule according to which every increase in glycemia must reduce it.

7. CONFLICTING EVIDENCE

A directly relevant but non-overlapping result was obtained in a kinetic study on 32 healthy subjects using hepatic or renal vein catheterization. During hyperglycemia of approximately 125 mg/dl above baseline, splanchnic insulin extraction did not change; renal extraction did not change either. The authors also observed that splanchnic extraction remained approximately constant within the physiological range of infused insulin concentrations and only decreased at supraphysiological concentrations exceeding 500 microU/ml [3].This evidence does not invalidate the correspondence between the analyzed study and the book section. Instead, it indicates that the effects depend on the experimental context: endogenous insulin secreted into the portal vein and infused insulin in the circulation do not reach the liver in the same way; furthermore, the intensity and duration of hyperglycemia, the outcome measure, and the component of clearance evaluated all vary. No directly conflicting evidence sufficiently relevant beyond this experimental difference has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent research and shows why results obtained with different protocols must be interpreted within their specific context.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Physiological experimental with hyperglycemic clamp	Eight healthy individuals	At 300 mg/dl, peripheral insulin increased more than the estimated secretion, consistent with reduced endogenous clearance.	direct confirmation	moderate
[1]	Physiological experimental with kinetic modeling	Healthy volunteers subjected to oral glucose, arginine, or a meal	Estimated hepatic extraction decreased from 67% to 42% with the increase in glucose-induced insulin exposure.	direct confirmation	moderate
[2]	Physiological experimental with direct hepatic venous sampling	Five healthy individuals	Approximately 80% of insulin was extracted during the first hepatic pass; the mass of secretory pulses predicted clearance.	direct confirmation	moderate
[3]	Physiological experimental with clamp and venous catheterization	Thirty-two healthy subjects	An increase in glycemia of approximately 125 mg/dl above baseline did not modify splanchnic or renal insulin extraction.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed shows that, under the experimental conditions considered, severe acute hyperglycemia can increase peripheral insulin more than the estimated pancreatic secretion, suggesting a reduction in endogenous insulin clearance. This finding is well supported by independent evidence describing the central and dynamic role of the liver in hormone extraction. It remains necessary to distinguish between secreted and infused insulin, between acute and prolonged responses, and between total clearance and hepatic extraction. The evidence does not allow for the reduction in clearance to be considered a universal response to glucose, nor for individual clinical consequences to be inferred.

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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