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ORIGINAL RESEARCH

The cellular biology of systemic insulin function - A review of the evidence

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1. ABSTRACT

The analyzed publication is a narrative review dedicated to the pathway of insulin in the body, from pancreatic secretion to degradation. For paragraph 2.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the relevant contribution concerns above all the hormone's first pass through the liver: a significant portion of the insulin secreted by the pancreas is captured and degraded by hepatocytes before reaching the muscles and adipose tissue.The study is not an original experiment on new participants, but integrates previous physiological, cellular, and clinical results. It describes the liver as a regulator of insulin bioavailability and links the reduction of insulin clearance to conditions of insulin resistance. Independent studies in humans confirm that hepatic extraction substantially modifies the amount of insulin that enters the systemic circulation and that lower clearance is often associated with lower insulin sensitivity. However, it remains prudent to distinguish association from causality: it has not been proven that reduced clearance, in isolation, causes type 2 diabetes.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 question addressed by the publication is how insulin is produced, transported, used, and finally eliminated in various organs. The general hypothesis is that each step of this process contributes to determining how much insulin is effectively available in the tissues and, therefore, to the control of glycemia.The point relevant to the book's paragraph concerns the liver. In simple terms, the pancreas does not decide on its own how much insulin circulates in the blood: the liver receives the hormone first through the portal vein and removes a portion of it before it reaches the peripheral circulation. The publication describes this process as hepatic insulin clearance, that is, the uptake, internalization, and degradation of insulin by liver cells.The research covered by the article can therefore support the passage stating that insulin concentration in the blood depends on both pancreatic secretion and the liver's ability to eliminate the hormone. However, it cannot, on its own, demonstrate the complete clinical sequence that leads from chronic hyperinsulinemia to type 2 diabetes, because it is a narrative review and not a prospective study designed to establish causal relationships in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review, meaning an interpretive analysis of the available literature by the authors, organized around the various stages of the insulin pathway: production in pancreatic beta cells, first-pass metabolism in the liver, action on blood vessels, entry into tissues, utilization in muscle and adipose tissue, and renal degradation.No new participants were enrolled, no new clinical interventions were performed, and no new experimental cohort is reported. A systematic literature search strategy, predetermined study inclusion criteria, a formal assessment of the risk of bias, or a meta-analysis are not described. This information is not reported in the available material, consistent with the narrative nature of the publication.For the topic examined here, the authors integrate human, animal, and cellular evidence regarding the arrival of insulin at the liver via the portal vein, its binding to the insulin receptor, clathrin-mediated endocytosis (the mechanism by which the cell engulfs molecules from the surface), and the degradation of the hormone. The publication also distinguishes between first-pass hepatic extraction and the subsequent passage of insulin already present in the systemic circulation.

4. RESULTS

The central finding, relevant to the book, is that the liver is the primary physiological filter for insulin secreted by the pancreas. Insulin reaches the portal vein at concentrations that can be much higher than those observed in peripheral blood. By passing through the hepatic sinusoids—small, highly permeable blood vessels in the liver—the hormone easily reaches the hepatocytes.The publication reports that, in humans, more than 50% of the insulin arriving from the portal vein can be degraded during the first hepatic pass, and in some measurements, up to approximately 80%. It also reports that a portion of the circulating insulin can be further removed during subsequent passes through the liver. The practical significance is straightforward: given the same level of pancreatic secretion, greater hepatic clearance reduces the insulin available in the periphery, while lower clearance tends to increase it.At the cellular level, insulin binds to its receptor on the hepatocyte membrane. The hormone-receptor complex is then internalized into the cell via endocytosis. The CEACAM1 molecule, a membrane protein involved in transferring the complex into the cell, and the IDE enzyme (insulin-degrading enzyme) are described as possible components of this process. However, the precise role of IDE in insulin clearance within the body remains controversial.The review also notes that, under conditions of insulin resistance, hepatic clearance may decrease. This reduction is presented as a possible adaptation: by eliminating the hormone more slowly, the body temporarily increases tissue exposure to insulin without necessarily having to immediately increase pancreatic secretion. However, this is a synthesis of previous studies and not a new result directly measured by the authors.

5. INTERPRETATION

The biological message is that the concentration of insulin in the blood is the result of two flows: the insulin released by the pancreas and the insulin

removed primarily by the liver. For this reason, a high blood insulin level alone does not allow us to deduce how much insulin has been secreted by the pancreatic beta cells.The publication provides a physiological basis consistent with the passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi: the liver regulates the bioavailability of the hormone before it reaches the muscles, adipose tissue, and other peripheral organs. The specifically documented pathway is therefore: pancreatic secretion arrival of insulin at the liver via the portal vein hepatic uptake and degradation lower quantity of the hormone in systemic circulation.A decrease in clearance can contribute to maintaining higher circulating insulin levels in the presence of a reduced tissue response to the hormone. However, this does not equate to proving that reduced clearance is always the primary event, nor that it inevitably causes insulin resistance. The relationship can be bidirectional and influenced by pancreatic secretion, body composition, liver function, diet, genetics, and the method used to estimate clearance.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the liver's filtering function comes from a physiological study conducted on five adults without diabetes, who underwent simultaneous sampling of the hepatic vein and an arterialized vein during fasting and glucose infusion. The authors estimated that approximately 80% of insulin was extracted during the first hepatic pass. During glucose infusion, absolute hepatic clearance increased from 1.06 ± 0.18 to 2.55 ± 0.38 pmol·kg–1·min–1; the extracted fraction, however, remained statistically similar, at 78.2 ± 4.4% versus 84.0 ± 3.9%. The mass of insulin secretory pulses was strongly associated with hepatic clearance, with a correlation of r = 0.81. This study confirms in humans that the liver rapidly modulates the amount of insulin that reaches peripheral tissues. The main limitation is the very small sample size and the absence of people with diabetes or obesity [1].A second study examined 91 adults with obesity and without diabetes, divided into three groups based on their degree of insulin resistance. The groups had comparable body mass indices but progressively lower insulin sensitivity. Endogenous insulin clearance decreased progressively from the most sensitive group to the most resistant one: the difference was already significant between the group with intermediate sensitivity and the most sensitive one, while at that stage, insulin secretion was not yet significantly increased. In the group with the highest insulin resistance, however, both clearance was reduced and secretion was increased. These data support the book's narrative as a possible adaptive sequence in obesity without diabetes, but the cross-sectional design does not allow for determining with certainty which alteration begins first in an individual's history [2].The available evidence therefore supports two distinct points. The first, more robust, is physiological: the liver directly determines how much insulin passes from the portal vein into the peripheral blood. The second, more cautious, is observational: in people with greater insulin resistance, clearance tends to be lower. The interpretation that this reduction in turn promotes chronic hyperinsulinemia is biologically plausible, but requires longitudinal and interventional studies to be defined as a causal relationship.

7. CONFLICTING EVIDENCE

An analysis conducted on 277 adults without diabetes, who were overweight or obese, suggests that a reduction in insulin clearance should not be attributed solely to adipose mass. Participants were classified based on obesity and insulin resistance using insulin suppression tests. Clearance was similar among people with and without obesity within the same level of insulin sensitivity. Conversely, insulin resistance and fasting insulinemia were associated with lower clearance, while body mass index did not show an independent association. The authors concluded that, in that sample, the reduced clearance in obesity was secondary to insulin resistance and not to the excess adiposity itself [3].This result does not contradict the liver's role in regulating circulating insulin. However, it scales back a simplistic interpretation of the obesity reduced clearance chain. Furthermore, it does not clarify whether insulin resistance causes the reduction in clearance, whether reduced clearance contributes to insulin resistance, or whether both phenomena are influenced by other factors. No further directly conflicting 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 publication that is the subject of the review from the independent research used to confirm or define the passage in the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Human, animal, and cellular literature	Describes the liver as the primary organ that captures and degrades a significant portion of secreted insulin.	biologically consistent evidence	moderate
[1]	Human physiological study	5 adults without diabetes	Approximately 80% of insulin was extracted during the first hepatic pass; clearance followed secretory peaks.	direct confirmation	moderate
[2]	Cross-sectional observational with metabolic tests	91 adults with obesity without diabetes	Clearance decreased progressively with increasing insulin resistance; in the intermediate group, it dropped before a significant increase in secretion.	indirect confirmation	moderate
[3]	Cross-sectional observational	277 adults without diabetes who are overweight or obese	Lower clearance was associated with insulin resistance, not with obesity independently of insulin sensitivity.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The passage in the book stating that insulin concentration depends on both pancreatic secretion and hepatic clearance is well-supported. The liver receives insulin first, eliminates a significant portion of it, and thus modulates the exposure of peripheral tissues to the hormone.It is also fairly well-supported that lower insulin clearance is associated with insulin resistance and may represent a compensatory response in certain stages of obesity without diabetes. However, it remains to be defined with greater precision whether this reduction is a cause, a consequence, or a parallel element of insulin resistance. The relationship with the progression toward type 2 diabetes therefore requires longitudinal and interventional 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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