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ORIGINAL RESEARCH

Variability of first-pass hepatic insulin extraction measured directly and its association with insulin sensitivity and plasma insulin - A review of the evidence

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1. ABSTRACT

The original study evaluated whether the proportion of insulin removed by the liver during its first pass through the portal circulation varied among healthy subjects and whether this variability was linked to fasting insulin and insulin sensitivity. In 12 healthy male dogs, first-pass hepatic extraction was measured using a direct experimental protocol based on insulin infusions into the portal vein and a peripheral vein. Extraction ranged from 22.4% to 77.2%; higher values were associated with greater insulin sensitivity and lower fasting insulin concentrations.The research contributes to the passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, which states that insulin clearance is an individual physiological characteristic and that plasma insulin does not automatically reflect pancreatic secretion alone. Independent studies in humans indicate that clearance contributes significantly to fasting insulin levels, has a hereditary component, and can decrease during modest weight gain. However, the causal link between reduced clearance and subsequent insulin resistance requires further longitudinal studies.

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2. ANALYZED STUDY

The research question was whether the liver, in addition to the pancreas, contributes to individual differences in blood insulin concentrations. The authors examined the hypothesis that greater first-pass hepatic extraction—that is, the amount of insulin removed by the liver before it reaches the rest of the body—is associated with better insulin sensitivity and lower fasting insulin levels.The connection to the book's section concerns precisely the significant individual variability in insulin clearance. The publication directly demonstrates that, in healthy animals kept under controlled experimental conditions, hepatic insulin extraction can differ greatly from one subject to another and that this difference is associated with the amount of hormone present in peripheral circulation.The study can document physiological associations in an animal model and use a direct measure of hepatic extraction. However, it cannot establish whether reduced extraction is the cause of insulin resistance, a consequence of it, or the result of common factors. Furthermore, it cannot automatically transfer the values measured in dogs to the human population.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study included 12 male mixed-breed dogs, approximately one year of age, with an average weight of 27.5 ± 1.0 kg. The animals were healthy, had liver function tests within the limits indicated by the authors, and were studied after overnight Fasting. Following a surgical procedure, a catheter was placed in the portal vein, the vessel that carries blood from the intestine and pancreas to the liver.Each dog underwent three randomized experiments while awake, separated by at least three days. Insulin sensitivity was estimated using the hyperinsulinemic-euglycemic clamp, a technique in which insulin is infused while glucose is kept stable; the amount of glucose required to maintain this stability indicates how well the body responds to insulin.First-pass hepatic extraction was calculated using two paired infusions. In one trial, insulin was infused into the portal vein, and in the other, into a peripheral vein. By comparing the insulin clearance rates in the two settings, the authors estimated the percentage removed by the liver during the first pass. They also measured the expression in the liver of INSR, the insulin receptor gene, and of CEACAM1 and IDE, proteins involved in cellular entry and insulin degradation, respectively.Associations between variables were analyzed using Spearman's correlation, indicated as rs. This index describes whether two variables tend to increase or decrease together, but it does not demonstrate a cause-effect relationship. To describe the distribution of hepatic extraction, the authors added baseline data from six other dogs from a previous equivalent protocol.

4. RESULTS

The main result was a wide variability in first-pass hepatic extraction. In the 12 dogs, the liver removed between 22.4% and 77.2% of the insulin it received through the portal vein; the mean value was 50.4 ± 19.1%. Including six dogs from a previous experiment, the mean in the 18 animals was 53.4%, with a standard deviation of 16.5 percentage points. In simple terms, healthy animals could eliminate very different amounts of insulin without showing overt glycemic alterations.Higher hepatic extraction was associated with greater whole-body insulin sensitivity: rs = 0.74; P = 0.006. The P-value indicates that, according to the statistical criterion adopted by the authors, the observed association was unlikely to be due to chance alone. Conversely, higher extraction was associated with lower fasting insulin concentrations: rs = –0.64; P = 0.03. Insulin sensitivity was also inversely associated with fasting insulin: rs = –0.67; P = 0.02.By excluding two dogs with particularly high fasting insulin levels from the analysis, the associations remained present and became stronger: hepatic extraction and insulin sensitivity rs = 0.82; P = 0.004; hepatic extraction and fasting insulin rs = –0.78; P = 0.008. This check reduces the risk that the entire result depends solely on two extreme observations, but it does not eliminate the limitation of the small sample size.The relationship with insulin sensitivity was primarily linked to the response of peripheral tissues, particularly muscle and adipose tissue. Hepatic extraction was positively associated with peripheral sensitivity, rs = 0.80; P = 0.002, but not with the liver's sensitivity in suppressing glucose production, rs = 0.31; P = 0.33. Hepatic expression of INSR was positively associated with extraction, rs = 0.67; P = 0.02; however, CEACAM1 and

IDE did not show statistically significant associations.

5. INTERPRETATION

The physiological significance is that the concentration of insulin in the blood depends on two processes: how much insulin the pancreas releases and how much is cleared, primarily by the liver. If the liver removes a smaller portion of the hormone, a greater amount can reach the general circulation even without a proportional increase in pancreatic secretion.The segment directly documented by the study is: individual differences in first-pass hepatic extraction differences in fasting insulin concentrations and insulin sensitivity. The positive association with INSR is biologically compatible with the fact that the insulin receptor participates in the uptake of the hormone by liver cells. However, the measurement of gene expression does not prove that the receptor is the cause of the observed differences.The research therefore supports the idea that clearance is not a secondary detail in the interpretation of insulinemia. However, it does not prove that low clearance causes insulin resistance. Since the study design is cross-sectional, both characteristics could depend on other physiological or metabolic determinants. Furthermore, extraction was measured in healthy dogs and not in people with obesity, prediabetes, or diabetes.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial confirmation in humans comes from an observational study conducted on 470 Hispanic-American adults without clinically manifest diabetes. Insulin metabolic clearance, measured during a hyperinsulinemic-euglycemic clamp, proved to be the strongest quantitative determinant of fasting insulin in a model that included insulin sensitivity, early secretion index, BMI, waist circumference, and glycemia. Overall, the variables considered explained 52% of the variability in fasting insulin levels. This result confirms the passage in the book stating that a high insulin value does not automatically equate to pancreatic hypersecretion [1].The individual component hypothesized in the book is supported by a family analysis of Hispanic-American cohorts. Insulin clearance showed heritability estimates ranging from 0.35 to 0.73, depending on the cohort and the measurement method. In simple terms, a significant portion of the differences observed between people was compatible with genetic contributions. This does not identify specific responsible genes nor does it exclude environmental influence, but it makes it plausible that clearance is a partially heritable physiological trait [2].A third study evaluated the role of modifiable metabolic factors by following 10 healthy men during an intentional increase of two BMI points, from 21.8 to 23.8 kg/m², over approximately four and a half months. After weight gain, basal insulin was higher; the authors' estimates indicated that reduced clearance contributed more to this change than increased secretion. After stimulation with a meal, oral glucose, or intravenous glucose, the increase in insulin was attributed to lower clearance, while C-peptide and estimated secretion did not change significantly. Although this was a very small sample consisting only of young men, the study supports the idea that clearance variability can also change in relation to early metabolic shifts [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contradictory results.However, there are significant interpretative limitations. The methods used in human studies often estimate whole-body insulin metabolic clearance, whereas the original study specifically measures first-pass hepatic extraction. Furthermore, clearance depends on the physiological context: fasting, meal, insulin concentration, body weight, and the degree of insulin resistance can all modify it. For this reason, the results do not justify considering a single fasting insulin measurement as proof of a single mechanism, nor do they allow for the deduction of a universal causal sequence.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent evidence selected for its relevance to individual variability in insulin clearance and its relationship with insulinemia and metabolic status.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal experimental, cross-sectional	12 healthy dogs; distribution extended to 18 with previous data	First-pass hepatic extraction from 22.4% to 77.2%; higher extraction associated with greater insulin sensitivity and lower fasting insulin	direct confirmation	moderate
[1]	Physiological observational	470 Hispanic-American adults without clinically manifest diabetes	Metabolic clearance was the quantitatively strongest determinant of fasting insulin in the multivariate model	direct confirmation	moderate
[2]	Family-based observational	Hispanic-American family cohorts without diabetes	Insulin clearance showed estimated heritability from 0.35 to 0.73	indirect confirmation	moderate
[3]	Non-randomized longitudinal intervention	10 healthy men subjected to modest weight gain	Reduced clearance contributed to the increase in basal insulin and explained the increase in stimulated insulin	biologically consistent evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed documents a high degree of variability in first-pass hepatic insulin extraction in healthy dogs. Greater extraction was associated with lower fasting insulinemia and higher insulin sensitivity. Independent evidence in humans confirms that clearance contributes substantially to differences in circulating insulin and can be influenced by hereditary and metabolic factors.The book's narrative is therefore moderately supported. The idea that plasma insulin does not exclusively measure pancreatic secretion is well-supported. Conversely, the hypothesis that reduced clearance regularly precedes and causes insulin resistance in people requires further 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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