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ORIGINAL RESEARCH

Relationship between disease severity, hyperinsulinemia, and impaired insulin clearance in patients with non-alcoholic steatohepatitis - Evidence review

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1. ABSTRACT

The original study compared 190 individuals without hepatic steatosis, with simple steatosis, or with non-alcoholic steatohepatitis to clarify why insulin levels are elevated in the blood. It found that, in people with fat accumulation in the liver, reduced hepatic insulin clearance was already present in simple steatosis and that insulin secretion did not differ significantly between simple steatosis and steatohepatitis.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, this finding helps explain why elevated insulinemia does not automatically equate to increased pancreatic production. Independent studies in adults, young people with obesity, and individuals with metabolic alterations support an association between higher liver fat, lower insulin clearance, and hyperinsulinemia. However, a small study with more detailed measurements did not confirm a direct link to liver fat, indicating that insulin resistance and measurement methods can alter the result. The relationship is therefore moderately supported, but it does not prove on its own that liver fat causes the defect in insulin clearance.

ONLINE ARTICLE

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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.

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2. ANALYZED STUDY

The research question was whether hyperinsulinemia—that is, a concentration of insulin in the blood higher than necessary—in people with fatty liver disease depends primarily on increased secretion by the pancreas or on reduced insulin clearance. Clearance is the process by which the body removes a hormone from circulation; the liver is the primary organ that eliminates newly secreted insulin.The publication is relevant to this section because it directly documents the essential point of the narrative: the amount of insulin detected in the blood depends on both the secretion of pancreatic beta cells and the rate of hormone elimination. In particular, it evaluates non-alcoholic fatty liver disease, or NAFLD (accumulation of fat in the liver not attributed to significant alcohol consumption), and its form involving inflammation and cellular damage, non-alcoholic steatohepatitis, or NASH.As a cross-sectional observational study, it compares conditions present during the same period and can therefore identify differences and associations between groups. It cannot establish with certainty whether liver fat caused the reduction in clearance, whether the clearance defect favored fat accumulation, or whether both result from other metabolic factors.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

According to the available abstract, 190 participants were included: 32 without NAFLD, 36 with simple steatosis, and 122 with NASH confirmed by liver biopsy. A biopsy is the microscopic analysis of a small tissue sample, which allowed for the assessment of the grade and stage of liver alterations.Insulin secretion and hepatic insulin clearance were estimated during an oral glucose tolerance test, which measures the body's response after glucose intake. Peripheral tissue insulin sensitivity and whole-body insulin clearance were measured using a euglycemic-hyperinsulinemic clamp, an experimental procedure considered the gold standard for quantifying how much insulin promotes glucose utilization and how rapidly it is cleared.The available material does not report the complete inclusion and exclusion criteria, the enrollment period, the distribution by sex and age, the absolute values of the main metabolic indicators, or the detailed statistical plan. Furthermore, no multivariate adjustments or follow-up data are reported, consistent with a cross-sectional design.

4. RESULTS

The most significant finding for this section of the book is that both individuals with simple steatosis and those with NASH had approximately 30% lower hepatic insulin clearance compared to individuals without NAFLD; the difference was statistically significant, with $P<0.01$. In practical terms, the liver removed less insulin from the blood as soon as fat accumulation was present, without the need for a more advanced histological picture.The reduction in hepatic clearance did not worsen significantly with increasing inflammation, cellular ballooning, or fibrosis. Ballooning indicates swollen and damaged liver cells; fibrosis is the formation of scar tissue. This result suggests that, in the sample studied, the hepatic defect in insulin elimination was more closely linked to the presence of steatosis than to the severity of these lesions.Whole-body insulin clearance, on the other hand, showed a progressive reduction as inflammation and ballooning worsened, with $P<0.001$ for the trend. Participants with NASH also had more marked hyperinsulinemia and adipose tissue insulin resistance compared to those with simple steatosis, while hepatic insulin sensitivity was similar between these two groups.No significant difference in insulin secretion was observed between simple steatosis and NASH. Therefore, in the comparisons made by the authors, the higher circulating insulin in NAFLD was more clearly associated with reduced elimination than with increased pancreatic production. The abstract does not report absolute values, confidence intervals, or numerical estimates of the association between hyperinsulinemia and clearance.

5. INTERPRETATION

The biological significance is straightforward: the insulin present in the blood is the result of two flows. The pancreas releases it into circulation, while the liver, in particular, intercepts and degrades it. If the latter process slows down, insulin levels can rise even when the pancreas is not necessarily producing more.The publication subject to this evidence review therefore documents the segment of hepatic steatosis

reduced hepatic insulin clearance increased blood exposure to insulin. It also documents that insulin secretion was not significantly different between simple steatosis and NASH. However, it does not prove that reduced clearance is the sole cause of hyperinsulinemia, nor that it always precedes insulin resistance or the progression of liver disease.The data on whole-body clearance requires further caution. The worsening associated with inflammation and ballooning may indicate that more active liver damage is accompanied by broader systemic metabolic impairment. However, even the authors could not fully distinguish a direct causal relationship from common factors, such as adiposity, diabetes, or insulin resistance in peripheral tissues.

6. INDEPENDENT CONFIRMING EVIDENCE

A first independent study examined 80 adults without diabetes, measuring liver fat using magnetic resonance spectroscopy and insulin clearance with a euglycemic-hyperinsulinemic clamp. Individuals with higher liver fat had approximately 40% higher insulin concentrations during the clamp and lower insulin clearance. The inverse relationship between liver fat and clearance remained significant after accounting for age, sex, and body mass index. This directly confirms the central association of the narrative, although it remains a cross-sectional study and therefore does not establish causality [1].Further confirmation comes from a multi-ethnic cohort of 632 young people with obesity, followed for two years. Intrahepatic fat was quantified via magnetic resonance imaging, and endogenous insulin clearance was estimated during oral glucose tolerance tests. Clearance decreased in individuals with NAFLD and across increasing tertiles of liver fat. Furthermore, an increase in liver fat at follow-up was associated with a decrease in clearance. The longitudinal design strengthens temporal consistency, but the estimates were derived from models based on glucose, insulin, and C-peptide, rather than a direct measurement of hepatic extraction [2].In a sample of 50 adults with overweight or obesity and mild metabolic alterations, the presence of steatotic liver disease associated with metabolic dysfunction was linked to higher insulinemia after oral glucose and lower insulin clearance. After adjusting for age, sex, and body mass index, a higher proportion of liver fat remained associated with both a greater incremental insulin response and lower clearance. This study supports the premise that postprandial hyperinsulinemia may be accompanied by reduced hormone clearance, but it has a limited sample size and does not separate the hepatic component from the extrahepatic one with the precision of a clamp [3].Taken together, these independent studies converge on the fact that liver fat and lower insulin clearance tend to occur together. This convergence spans both adults and young people and utilizes different techniques. However, none of these studies demonstrate that reducing liver fat necessarily restores clearance or that reduced clearance is the primary event in the metabolic sequence.

7. CONFLICTING EVIDENCE

A small cross-sectional study compared 13 people without diabetes with NAFLD and 15 controls matched for age and body mass index. Using computed tomography, oral glucose tolerance tests, and tracer-based clamps, it found no significant differences in hepatic insulin extraction or extrahepatic clearance between the groups. Instead, hepatic extraction was positively associated with muscle and adipose insulin sensitivity, but not with liver fat content [4].This result does not deny that total clearance may be reduced in NAFLD, but it challenges the more linear interpretation that liver fat alone directly determines lower insulin disposal. The differences compared to the original study may depend on the very small sample size, the radiological definition of steatosis, the absence of biopsy, and the fact that hepatic extraction and total clearance are not overlapping measures.No further directly conflicting evidence of sufficient relevance was identified; this does not prove the absence of contradictory results. Differences between measurement techniques, the degree of insulin resistance, the presence of diabetes, and population characteristics remain important elements for interpreting the literature.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study covered by the review from the independent publications used to confirm or define the scope of the paragraph's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cross-sectional observational with metabolic measurements and biopsy	190 adults: 32 without NAFLD, 36 with simple steatosis, 122 with NASH	Hepatic clearance approximately 30% lower in simple steatosis and NASH compared to no NAFLD; secretion similar between simple steatosis and NASH	direct confirmation	moderate
[1]	Cross-sectional observational with clamp	80 adults without diabetes	Higher liver fat associated with lower insulin clearance and approximately 40% higher insulinemia during clamp	direct confirmation	moderate
[2]	Cross-sectional and longitudinal observational cohort	632 young people with obesity, followed for two years	Higher intrahepatic fat associated with lower insulin clearance; increase in fat at follow-up associated with further decrease in clearance	direct confirmation	moderate
[3]	Cross-sectional observational	50 adults with overweight or obesity and mild metabolic alterations	MAFLD associated with hyperinsulinemia after oral glucose and lower insulin clearance	indirect confirmation	moderate
[4]	Cross-sectional observational with clamp and tracers	13 adults without diabetes with NAFLD and 15 matched controls	No significant difference in hepatic insulin extraction between NAFLD and controls; association with insulin sensitivity, not with liver fat	conflicting evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

Reduced insulin clearance represents a biologically plausible and moderately supported explanation for the hyperinsulinemia observed in many people with hepatic steatosis. The analyzed study shows that this phenomenon can be present as early as in simple steatosis and does not necessarily coincide with increased pancreatic secretion.Independent evidence confirms the association between higher liver fat and lower insulin elimination across different populations. However, the results do not prove a unidirectional causality: insulin resistance, adiposity, inflammation, and individual characteristics may all contribute simultaneously. For this reason, elevated plasma insulin should not be interpreted, on its own, as proof of beta-cell hypersecretion.

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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