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ORIGINAL RESEARCH

Insights into circulating CEACAM1 in insulin clearance and disease progression: evidence from the Portuguese PREVADIAB2 study - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether the blood concentration of CEACAM1, a protein involved in the hepatic clearance of insulin, reflects alterations in insulin metabolism in 1,019 adults from the Portuguese PREVADIAB2 cohort. As subjects progressed from normoglycemia to prediabetes and type 2 diabetes, body mass index, insulin resistance, insulinemia, and the frequency of hepatic steatosis increased, while circulating levels of CEACAM1 were found to be lower compared to normoglycemia.In the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that more compromised metabolic profiles also exhibit a lower capacity to clear insulin, and that this relationship is more recognizable in less compromised subjects. Independent studies in humans confirm that obesity and fat accumulation in the liver are associated with a reduction in insulin clearance; animal models also support a possible causal role for the loss of hepatic CEACAM1. However, the cross-sectional design does not establish the temporal sequence in humans, and circulating CEACAM1 is not yet a clinically validated biomarker.

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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.

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 research question was whether blood levels of CEACAM1, a glycoprotein primarily found in liver cells, could reflect the body's ability to clear insulin. This elimination, known as *insulin clearance*, prevents the hormone from remaining in circulation longer than necessary.The hypothesis was biologically plausible: in the liver, CEACAM1 participates in the entry of the insulin-receptor complex into the cell, a necessary step for the degradation of the hormone. The study is relevant to section 3.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it evaluates, in a human population, whether a profile characterized by greater adiposity, hepatic steatosis, and insulin resistance is accompanied by lower insulin clearance and lower levels of circulating CEACAM1.The publication documents associations observed at a single point in time. It can therefore show that certain metabolic characteristics tend to occur together, but it cannot prove that the decrease of CEACAM1 in the blood causes the reduction in insulin clearance, nor that the latter necessarily precedes diabetes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors analyzed a cross-sectional cohort—a snapshot of health status collected over a specific period—consisting of 1,019 participants from the Portuguese PREVADIAB2 program. The median age was 62 years, and 60% of the participants were women. In 2014, all participants underwent an oral glucose tolerance test with 75 g of glucose, with blood samples taken at fasting, 30 minutes, and 120 minutes.Based on the 2019 World Health Organization criteria, 735 individuals had normoglycemia, 226 had prediabetes, and 58 had newly diagnosed type 2 diabetes. Subjects already diagnosed and pharmacologically treated for diabetes and those without available biological samples were excluded. CEACAM1 was measured in the serum using ELISA, an immunological technique that quantifies a protein using specific antibodies.The authors estimated fasting and early post-glucose insulin secretion, fasting insulin clearance, and insulin resistance using HOMA-IR, an index calculated from fasting glycemia and insulin. They also used the Fatty Liver Index, an indirect index of probable hepatic steatosis. Differences between groups were evaluated using non-parametric tests; data are reported as median and interquartile range. A hierarchical analysis classified 945 participants—those with complete data for all included variables—into four metabolic profiles.

4. RESULTS

Worsening glucose tolerance was accompanied by a less favorable metabolic profile. The median BMI increased from 26 kg/m² in normoglycemia to 28 in prediabetes and 29 in type 2 diabetes. The proportion of individuals with a Fatty Liver Index of at least 60, indicative of a high probability of steatosis, increased from 26% to 46% and 60%. HOMA-IR also increased from 1.2 to 1.9 and 2.5: a higher value indicates greater insulin resistance.Fasting insulin increased from 5.8 µIU/mL in normoglycemic individuals to 8.5 in prediabetes and 10.0 in diabetes. In the same comparison, estimated basal insulin secretion increased from 143 to 180 and 215 pmol/min. Conversely, the early insulin response to glucose decreased: the insulinogenic index went from 0.73 in normoglycemia to 0.45 in prediabetes and 0.26 in diabetes. Simply put, as metabolic damage increased, the pancreas produced more fasting insulin but responded less readily to glucose.The result most relevant to the book concerns insulin clearance and CEACAM1. The median circulating CEACAM1 was 29.8 ng/mL in normoglycemia, 26.6 ng/mL in prediabetes, and 27.3 ng/mL in diabetes; the differences compared to normoglycemia were statistically significant. In prediabetes, fasting insulin clearance was lower than in normoglycemia, with median values of 3.8 versus 4.0 L/min; clearance during the glucose tolerance test was also lower, 0.16 versus 0.17. In the newly diagnosed diabetes group, however, clearance was not further reduced.In the analysis by metabolic profiles, the group with the worst overall picture, representing 25% of the classified participants, had the highest BMI, a greater prevalence of steatosis, higher HOMA-IR, and the lowest clearance. Compared to the most metabolically favorable group, it had a fasting clearance of 3.1 versus 4.9 L/min and CEACAM1 levels of 26.3 versus 27.5 ng/mL. Positive correlations between CEACAM1 and clearance were more recognizable in the less compromised clusters, but the authors themselves

note that their intensity was low and varied between groups.

5. INTERPRETATION

The primary significance is that hyperinsulinemia, meaning an elevated amount of insulin in the blood, does not depend solely on how much insulin is produced by the pancreas. It also depends on how quickly the liver and other organs remove it from circulation. In the Portuguese cohort, profiles associated with greater adiposity, hepatic steatosis, and insulin resistance showed, on average, lower insulin clearance.The segment specifically documented by the publication is therefore: lower efficiency in insulin elimination associated with a more compromised metabolic profile, with a relationship between circulating CEACAM1 and clearance that is more recognizable in people with normoglycemia or less metabolic impairment. This is why the study appears in the section dedicated to insulin clearance and hyperinsulinemia.The biological interpretation proposed by the authors is that lower levels of CEACAM1 in the blood may reflect lower availability of the same protein in the liver. However, blood levels do not indicate with certainty the quantity or activity of CEACAM1 in liver cells. Furthermore, other processes can modify clearance, including insulin-degrading enzymes and renal elimination. For this reason, circulating CEACAM1 should be considered a promising association, not diagnostic or causal evidence.

6. INDEPENDENT SUPPORTING EVIDENCE

Particularly relevant human confirmation comes from two independent cohorts studied by Fu and colleagues. The first included 460 participants evaluated with an oral glucose tolerance test; in the second, 81 people underwent intravenous tests and a hyperinsulinemic-euglycemic clamp, a procedure that more directly measures insulin sensitivity and hormone dynamics. All obese participants showed lower insulin clearance compared to lean controls. Among obese individuals without diabetes, clearance decreased progressively as insulin resistance worsened, while secretion did not increase in the early stages. This directly confirms the passage in the book stating that reduced insulin elimination can contribute early on to the hyperinsulinemia associated with obesity [1]. The limitation is that this work is also primarily observational and does not demonstrate which biological alteration initiates the process.A second human study examined 190 people, including 32 without hepatic steatosis, 36 with simple steatosis, and 122 with biopsy-confirmed steatohepatitis. Hepatic insulin clearance was approximately 30% lower in both simple steatosis and steatohepatitis compared to controls without steatosis. There was no significant difference in insulin secretion between simple steatosis and steatohepatitis. This reinforces the link between increased steatosis and reduced hepatic insulin elimination presented in the book's narrative [2]. However, the result does not prove that liver fat is the sole cause of reduced clearance, because adiposity and insulin resistance can occur simultaneously.The relationship between hepatic CEACAM1, clearance, and metabolic consequences is experimentally supported by a mouse model with liver-specific Ceacam1 deletion. The mice first developed reduced insulin clearance and hyperinsulinemia as early as two months, followed by hepatic insulin resistance and steatohepatitis around seven months [3]. This sequence causally supports the chain of reduced hepatic CEACAM1 function reduced clearance hyperinsulinemia metabolic alterations in the animal model. This is an important mechanistic confirmation, but it does not prove that CEACAM1 measured in human blood has the same function or the same prognostic value.

7. CONFLICTING EVIDENCE

The relationship does not appear uniform across every metabolic condition. In the same original study, insulin clearance was reduced in prediabetes but not in the group with newly diagnosed type 2 diabetes; furthermore, some clusters showed reduced clearance without particularly low levels of CEACAM1. This indicates that the link between the circulating protein and clearance depends on the clinical context and cannot be interpreted as a constant one-to-one ratio.A study of 70 women with gestational diabetes and 70 pregnant women with normal glucose tolerance did not find a statistically significant difference in mean CEACAM1 levels between the groups. Within the gestational diabetes group, however, higher CEACAM1 was associated with greater insulin sensitivity and lower insulin levels after a meal [4].

This evidence does not contradict the biological plausibility of the protein, but it scales back the idea that its circulating value reliably identifies every form of dysglycemia or insulin resistance.No directly conflicting evidence sufficiently relevant to the specific relationship between circulating CEACAM1 and insulin clearance in non-pregnant adults has been identified; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the observational data from the analyzed publication from independent confirmations and the evidence that defines its generalizability limits.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cross-sectional observational	1,019 adults from the PREVADIAB2 cohort	Prediabetes and worse metabolic profiles associated with lower insulin clearance and lower circulating CEACAM1; relationship more recognizable in less compromised subjects	direct confirmation	moderate
[1]	Observational with two cohorts and complementary physiological measurements	460 participants in the first cohort and 81 in the second	In obesity, insulin clearance was reduced; in the early stages of insulin resistance, it decreased before the increase in secretion	direct confirmation	moderate
[2]	Clinical observational	190 adults with no steatosis, simple steatosis, or steatohepatitis	Simple steatosis and steatohepatitis associated with approximately a 30% reduction in hepatic clearance compared to controls	direct confirmation	moderate
[3]	Experimental animal	Mice with hepatic Ceacam1 deletion and controls	Lower clearance and hyperinsulinemia preceded hepatic insulin resistance and steatohepatitis	biologically consistent evidence	moderate

[4]	Clinical observational	70 women with gestational diabetes and 70 pregnant women with normal tolerance	No significant difference in CEACAM1 between groups; in gestational diabetes, higher CEACAM1 associated with greater insulin sensitivity	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed pertinently supports the narrative that hyperinsulinemia does not depend exclusively on pancreatic secretion: reduced insulin clearance contributes to the metabolic profile associated with obesity, steatosis, and insulin resistance. This part of the narrative is moderately supported by independent evidence in humans.The possible role of CEACAM1 is well-supported at a mechanistic level in animal models. In humans, however, circulating levels of the protein currently represent a promising observational signal, but not a validated diagnostic test. Longitudinal studies are needed to verify whether CEACAM1 truly anticipates the reduction in clearance or the progression toward diabetes and steatosis.

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] **Impaired Insulin Clearance as the Initial Regulator of Obesity-Associated Hyperinsulinemia: Novel Insight Into the Underlying Mechanism Based on Serum Bile Acid Profiles**
Fu et al., 2022
Diabetes Care
DOI: https://doi.org/10.2337/dc21-1023

[2] **Relationship between disease severity, hyperinsulinemia, and impaired insulin clearance in patients with nonalcoholic steatohepatitis**
Bril et al., 2014
Hepatology
DOI: https://doi.org/10.1002/hep.26988

[3] **Hyperinsulinemia drives hepatic insulin resistance in male mice with liver-specific Ceacam1 deletion independently of lipolysis**
Ghadieh et al., 2019
Metabolism
DOI: https://doi.org/10.1016/j.metabol.2019.01.008

[4] **Association of circulating CEACAM1 levels and insulin sensitivity in gestational diabetes mellitus**
Wu et al., 2020
BMC Endocrine Disorders
DOI: https://doi.org/10.1186/s12902-020-00550-3