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Chronic hyperinsulinemia promotes meta-inflammation and extracellular matrix deposition in adipose tissue: implications of nitric oxide - A review of the evidence

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1. ABSTRACT

The analyzed study examined whether a persistent excess of insulin in the blood can directly contribute to inflammation of adipose tissue, the tissue that stores energy in the form of fat. In mice treated with insulin for eight weeks, the authors observed more pro-inflammatory immune cells, fewer populations with regulatory functions, and increased deposition of extracellular matrix, the network of proteins that physically supports tissues. In obese models, a partial reduction in circulating insulin was associated with less adipose inflammation and improved insulin sensitivity.The research contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which suggests that hyperinsulinemia can act as an active factor in metabolic inflammation, not just as its consequence. Independent evidence shows that insulin can increase inflammatory signals in human adipose tissue and that preventing hyperinsulinemia in mice is associated with reduced inflammation. However, experimental data also indicate that reducing macrophage recruitment does not always improve insulin sensitivity. The most prudent conclusion is therefore that the mechanism is well-supported in experimental models, while it requires long-term clinical confirmation in humans.

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 chronic hyperinsulinemia, i.e., a persistently high concentration of insulin in the blood, can in itself promote inflammation of adipose tissue and the metabolic alterations associated with obesity. The hypothesis was relevant because, in obesity and type 2 diabetes, elevated insulin can be both a compensatory response to the reduced effectiveness of the hormone and a possible factor that worsens the metabolic profile.The relevance to paragraph 5.2 is specific. The analyzed publication experimentally tests the segment of the narrative according to which a persistent increase in insulin can precede and promote inflammatory changes in visceral fat. It does not prove that this happens with the same sequence, intensity, or duration in people with obesity. Instead, it demonstrates, in murine models, that modifying exposure to insulin can simultaneously alter immune cells, the extracellular matrix, and the metabolic response of adipose tissue.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used mice subjected to continuous exogenous insulin infusion for eight weeks via osmotic mini-pumps, small devices that release a substance at a constant rate. To evaluate the opposite effect, they partially reduced insulin production by destroying a portion of pancreatic beta cells with streptozotocin, a substance used experimentally to reduce the mass of insulin-producing cells.The reduction of insulin was studied in two obesity contexts: mice with diet-induced obesity and db/db mice, a genetic model characterized by severe obesity and metabolic alterations. In the epididymal white fat, a visceral deposit in the mouse, the authors isolated the stromal vascular fraction, which is the set of non-adipose cells that includes immune cells. They then used flow cytometry, a technique that counts and characterizes cells based on their markers, to quantify immune populations.The role of iNOS, the inducible nitric oxide synthase, an enzyme that can increase nitric oxide production during inflammation, was also evaluated. Mice lacking the iNOS gene were used. The available material is only the abstract: group size, sex and age of the animals, insulin dosage, exclusion criteria, control details, statistical analyses, significance values, and complete data on energy consumption are not reported in the available material.

4. RESULTS

In mice chronically exposed to insulin, adipose tissue showed a more inflammatory profile. M1 macrophages and NK cells—two populations generally associated with pro-inflammatory signals—increased. Conversely, M2 macrophages, eosinophils, and regulatory T cells—cells that in many contexts help to limit or regulate inflammation—decreased. This M1/M2 distinction is a useful simplification, but it does not capture the full variety of macrophages present in adipose tissue.The shift in immune populations was accompanied by a worsening of the metabolic phenotype associated with obesity. The abstract does not report absolute values, percentage changes, P-values, or quantitative measures of insulin sensitivity; therefore, it is not possible to estimate the precise magnitude of the effects from the available material.In the pathway proposed by the authors, the higher prevalence of M1 macrophages compared to M2 favored an imbalance between iNOS and arginase-1, an enzyme often associated with tissue repair functions. This imbalance was linked to increased extracellular matrix deposition and the development of insulin resistance in adipose tissue. In simple terms, the fat appeared more infiltrated by pro-inflammatory immune cells and stiffer due to the accumulation of structural components.Partial reduction of circulating insulin in obesity models attenuated the inflammation induced by caloric excess and improved insulin sensitivity. Furthermore, in mice lacking iNOS, the M1:M2 imbalance, extracellular matrix deposition, and insulin resistance attributed by the authors to hyperinsulinemia were not observed. These results support an experimental role for iNOS in the model, but they do not establish that the enzyme is the only relevant mediator in humans.

5. INTERPRETATION

The primary biological significance is that insulin, beyond its physiological role in facilitating glucose entry into cells, can contribute to altering the microenvironment of adipose tissue when it remains elevated for a long time. In the mouse model studied,

this change included an increase in pro-inflammatory immune cells, a reduction in regulatory populations, and an accumulation of extracellular matrix.The sequence documented directly by the publication is: experimental chronic hyperinsulinemia alteration of immune populations in adipose tissue increased extracellular matrix deposition and reduced insulin sensitivity. The part relating to the partial reduction of insulin strengthens the causal hypothesis because it modifies exposure and observes changes in the opposite direction. However, in obesity models, insulin reduction can also influence body weight, lipid metabolism, and other biological pathways; therefore, it does not allow for attributing every improvement exclusively to reduced inflammation.The main limitation is transferability. The experiments were conducted in mice, and the full text is not available to verify sample size, effect size, and possible confounding factors. The work therefore supports a plausible and experimentally tested pathogenic mechanism in mice, not a clinical demonstration that hyperinsulinemia is always the primary cause of metabolic inflammation in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial confirmation concerns the direct effect of insulin on human adipose tissue. In nine healthy volunteers subjected to a hyperinsulinemic-euglycemic clamp—a procedure that maintains stable glycemia while controlledly increasing insulin—interleukin-6 gene expression in subcutaneous fat increased 11-fold after two hours, 3-fold after four hours, and 5-fold after six hours. TNF-alpha gene expression also increased in the adipose tissue. The study provides experimental evidence in humans that insulin can rapidly increase inflammatory markers in fat, but it does not evaluate chronic exposure or the onset of obesity or diabetes [1].Pedersen and colleagues examined 36 people with obesity and observed a positive association between circulating insulin and inflammatory genes in visceral adipose tissue, regardless of body mass index. The most informative part regarding a causal link, however, is experimental: in the same lines of research, lowering circulating insulin by approximately 50% in obese mice reduced macrophage content and inflammatory signals in fat; furthermore, insulin infusion in lean mice, maintained at euglycemia, increased cytokine expression in adipose tissue. This convergence links hyperinsulinemia to adipose inflammation in both human observation and murine intervention [2].Further independent evidence comes from a genetic model. Mehran and colleagues genetically reduced the ability to develop hyperinsulinemia in mice fed a high-fat diet. Animals with lower insulin production were protected from diet-induced obesity and exhibited adipose tissue with smaller adipocytes, less inflammation, and reduced fatty acid leakage. This study confirms that preventing hyperinsulinemia can alter the metabolic and inflammatory trajectory, but the result is intertwined with the prevention of weight gain: it does not completely isolate inflammation as the sole mechanism [3].Taken together, these independent studies support a coherent chain: elevated insulin can increase inflammatory signals in adipose tissue; in mice, limiting hyperinsulinemia reduces inflammatory markers and certain metabolic consequences. Confirmation is more direct in murine experiments, while in humans it remains limited to acute effects and tissue associations.

7. CONFLICTING EVIDENCE

Relevant evidence suggests that we should not automatically view the sequence of adipose inflammation insulin resistance as a single, mandatory relationship. In mice fed a high-fat diet, the selective blockade of interleukin-6 trans-signaling prevented macrophage recruitment in adipose tissue, but did not improve insulin action. In other words, reducing a specific pathway for macrophage entry into fat was not sufficient to correct insulin resistance in that model [4].This result does not directly contradict the observation that hyperinsulinemia can promote adipose inflammation. However, it does scale back the interpretation that any reduction in inflammation or a single immune population must necessarily translate into an improvement in insulin sensitivity. The relationship depends on the model, the duration of obesity, the immune signals involved, and other factors, including lipid overload in tissues.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from the independent publications used to verify the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal, insulin intervention and obesity models	Mice with insulin infusion; diet-induced obesity and db/db models; iNOS-deficient mice	Chronic hyperinsulinemia increased the pro-inflammatory immune profile and matrix deposition in fat; reducing insulin attenuated inflammation and insulin resistance.	direct confirmation	moderate
[1]	Human physiological intervention	Nine healthy volunteers undergoing hyperinsulinemic-eug lycemic clamp	Acutely elevated insulin increased IL-6 and TNF-alpha expression in subcutaneous adipose tissue.	biologically consistent evidence	moderate
[2]	Human observational, cellular and animal	36 people with obesity; obese and lean mice; cultured adipocytes	Higher insulin was associated with greater adipose inflammation; reducing insulin in obese mice decreased macrophages and inflammatory markers.	direct confirmation	moderate
[3]	Genetic animal	Mice with reduced capacity to develop hyperinsulinemia fed a high-fat diet	Prevention of hyperinsulinemia protected against diet-induced obesity and was associated with lower fat inflammation.	indirect confirmation	moderate
[4]	Animal, immune signaling intervention	Mice on a high-fat diet with interleukin-6 trans-signaling blockade	Reduction of macrophage recruitment in fat did not improve insulin action.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, in mice, that chronic hyperinsulinemia can promote an inflammatory environment in adipose tissue, accompanied by extracellular matrix remodeling and reduced insulin sensitivity. Its citation in the book's paragraph is therefore consistent with the experimental result actually documented.Independent evidence makes the narrative reasonably well-supported: in humans, insulin can rapidly increase certain inflammatory signals in fat, while in mouse models, reducing or preventing hyperinsulinemia is associated with less adipose inflammation. It remains necessary to distinguish the contribution of insulin from that of energy excess, weight gain, lipids, and various immune pathways. It has not yet been proven that every condition of hyperinsulinemia produces the same causal chain in humans as observed in mice.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **A major role of insulin in promoting obesity-associated adipose tissue inflammation**
Pedersen et al., 2015
Molecular Metabolism
DOI: https://doi.org/10.1016/j.molmet.2015.04.003

[2] **Hyperinsulinemia Drives Diet-Induced Obesity Independently of Brain Insulin Production**
Mehran et al., 2012
Cell Metabolism
DOI: https://doi.org/10.1016/j.cmet.2012.10.019

[3] **Blocking IL-6 trans-Signaling Prevents High-Fat Diet-Induced Adipose Tissue Macrophage Recruitment but Does Not Improve Insulin Resistance**
Kraakman et al., 2015
Cell Metabolism
DOI: https://doi.org/10.1016/j.cmet.2015.02.006

[4] **Insulin stimulates interleukin-6 and tumor necrosis factor-a gene expression in human subcutaneous adipose tissue**
Krogh-Madsen et al., 2004
American Journal of Physiology-Endocrinology and Metabolism
DOI: https://doi.org/10.1152/ajpendo.00274.2003