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Macrophages, low-grade inflammation, insulin resistance, and hyperinsulinemia: a reciprocal and ambiguous relationship in the development of metabolic diseases - Evidence review

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1. ABSTRACT

The analyzed publication is a narrative review dedicated to the bidirectional relationship between chronic low-grade inflammation, insulin resistance, hyperinsulinemia, and macrophages. The authors describe how these immune cells possess insulin receptors and can modify their activity in response to insulin signaling. The review does not present a new experiment, a new patient cohort, or a quantitative meta-analysis.In section 5.2 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that persistent exposure to high insulin levels can alter the immune regulation of macrophages, promoting circuits that maintain inflammation and metabolic dysfunction. Independent studies in human monocytes, mouse models, and cell cultures support some steps of this chain. However, other experiments show anti-inflammatory or M2-like responses, indicating that the effect is not uniform. The most prudent conclusion is that the circuit is biologically plausible and moderately supported, but not unequivocally proven in humans.

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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 research question was to understand if and how macrophages, immune cells that remove microorganisms, cellular debris, and excess lipids, participate in the reciprocal relationship between metabolic alterations and inflammation. The hypothesis discussed is that insulin resistance and metabolic damage may make macrophages more prone to producing inflammatory signals and that, in turn, these signals worsen the tissue response to insulin.The relevance to section 5.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns, above all, a segment of the chain: macrophages express the insulin receptor, and persistent exposure to high concentrations of this hormone can modify their regulatory signals, in some conditions increasing the response to pro-inflammatory stimuli.The publication does not demonstrate that hyperinsulinemia is always the primary event in metabolic diseases, nor does it prove that it has the same effect in every tissue or in every person. As it is a review, its contribution consists of connecting previously published results and describing a possible network of biological interactions, not in establishing a clinical causal relationship on its own.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The original study is a narrative review of the scientific literature, with a particular focus on adipose tissue and the liver. The authors selected experimental and observational examples regarding insulin signaling in macrophages, the recruitment of immune cells into metabolically stressed tissues, and the role of pro-inflammatory cytokines, which are proteins that transmit signals between cells.No systematic review protocol is reported. There is no mention of the databases consulted, search strings, formal inclusion and exclusion criteria, the period of the bibliographic search, standardized risk of bias assessment, or meta-analysis. There are no participants enrolled directly by the authors, treatment groups, follow-ups, or clinical endpoints specific to the publication.The review discusses results obtained in humans, mice, isolated macrophages, monocytes, and cell lines. This variety is useful for reconstructing a possible mechanism, but it requires caution: a change observed in cultured cells or in a mouse does not automatically equate to a proven clinical effect in people.

4. RESULTS

The central biological message is that macrophages are not mere spectators of metabolism. Under physiological conditions, they contribute to tissue repair and the removal of lipids or damaged cells. When adipose tissue or the liver is subjected to prolonged energy overload, however, stress signals, lipids, and inflammatory mediators can accumulate, altering the activity of these cells.The review describes how the insulin receptor utilizes intracellular pathways shared with immune signals. Among these are PI3K/Akt, a sequence of proteins that regulates metabolism, survival, and cellular response, and MAPK, a family of signals involved in the response to stress and inflammation. The authors report that the activation of Akt1 can promote regulatory and anti-inflammatory signals, while other nodes, including Akt2 and MAPK, can support pro-inflammatory responses in specific contexts.The publication also summarizes data suggesting that insulin can increase, in some models, the production of TNFα, IL-1β, and IL-6, three pro-inflammatory cytokines. However, it also describes experiments in which insulin increased IL-10, a cytokine generally associated with limiting inflammation, and reduced certain inflammatory signals. No new absolute values, confidence intervals, or P-values are presented by the authors of the review, as such data belong to the primary studies discussed.The result most relevant to the book is therefore qualitative and mechanistic: abnormal metabolic exposure, which includes hyperinsulinemia and insulin resistance, can shift the balance of macrophages toward functions that maintain inflammation; the resulting inflammation can, in turn, aggravate insulin resistance.

5. INTERPRETATION

In simple terms, insulin does not only act on cells that manage glucose and fats. It can also modify the behavior of immune cells. If this regulation remains balanced, it can contribute to the normal response to damage and tissue repair. If, however, the metabolic environment remains altered over time, the system can enter a reinforcing loop: distressed tissues activate

macrophages, macrophages release inflammatory mediators, and these make the response to insulin more difficult.The segment actually documented by the publication subject to the Evidence Review is the link between insulin signaling in macrophages, their functional polarization, and the possible amplification of inflammatory signals. Polarization should not be understood as a rigid division between "good" and "bad" macrophages: the M1 and M2 definitions are simplified models, and cells present in metabolically altered tissues often show mixed characteristics.The broader interpretation, according to which hyperinsulinemia represents a primary pathogenetic determinant in every stage of obesity or type 2 diabetes, goes beyond what this review can demonstrate. The authors themselves emphasize that the issue of the temporal order between metabolic stress, insulin resistance, and inflammation is not definitively resolved. The relationship appears reciprocal, tissue-dependent, and dependent on the duration of exposure.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct confirmation in humans at the cellular level comes from a study on primary monocytes, which are circulating precursors of macrophages, obtained from healthy volunteers. Acute exposure to insulin activated PI3K/AKT/mTOR, a pathway that coordinates energy use and cellular functions, and increased the secretion of IL-6 induced by lipopolysaccharide, a bacterial component used experimentally to stimulate innate immunity. After 24 hours of insulin exposure, the monocytes showed an increase in lipopolysaccharide-induced TNFα production and greater migration toward MCP-1. The study also observed a positive association between plasma insulin and the number of macrophages in the adipose tissue of overweight individuals. The experiment supports the transition “elevated insulin increased pro-inflammatory reactivity,” but it does not prove that this effect causes metabolic disease in the general population [1].A second study in mice identified a more specific step in the regulatory chain. In macrophages from obese animals, hyperinsulinemia reduced the expression of IRS2, a protein that transmits part of the insulin receptor signal. The reduction of IRS2 compromised the response to IL-4, a signal normally involved in macrophage repair and regulatory programs. Mice with IRS2 deletion in myeloid cells developed greater inflammation in the liver and adipose tissue and insulin resistance when fed a high-fat diet. This causally links, in mice, hyperinsulinemia, altered macrophage signaling, and metabolic worsening; however, it does not constitute clinical proof in humans [2].A third genetic experiment in mice reinforces the idea that insulin signaling in myeloid cells contributes to the inflammatory circuit of obesity. By eliminating the insulin receptor in myeloid lineage cells, animals exposed to a high-fat diet maintained weight gain similar to controls, but showed less macrophage accumulation in adipose tissue, fewer local inflammatory signals, and less deterioration of insulin sensitivity. The result suggests that, in that model, insulin signaling in immune cells promotes macrophage recruitment and obesity-associated inflammation. The main limitation is that genetic manipulation does not simply reproduce human hyperinsulinemia and may have effects specific to the model [3].Confirmation at the tissue level comes from research that integrated human samples, obese mice, and cultured adipocytes. In 36 people with different body mass index values, higher concentrations of circulating insulin were associated with greater expression of CCL2, IL6, TNFα, and IL1B in adipose tissue, even after accounting for body mass index. In mice, the reduction of circulating insulin attenuated adipose inflammation and improved insulin sensitivity; the infusion of insulin into lean mice kept euglycemic increased cytokine expression in adipose tissue. In adipocytes, insulin increased CCL2 through ERK, a signal that can promote the recruitment of immune cells. This evidence supports the context of the immuno-metabolic circuit, but does not attribute the entire effect directly to macrophages [4].

7. CONFLICTING EVIDENCE

There are relevant findings that suggest caution. In a study on murine macrophages rendered insulin-resistant through chronic insulin exposure or alterations in signaling components, the cells developed an M2-like phenotype, with a reduced response to lipopolysaccharide and lower production of pro-inflammatory signals following stimulation. The authors also observed an increase in mTORC1 activity and glycolysis, i.e., the use of glucose through

a rapid energy pathway [5].This result does not deny that elevated insulin can promote inflammation in other contexts. Rather, it shows that macrophage insulin resistance, chronic exposure to the hormone, and inflammatory activation do not produce a uniform response. The origin of the cell, the presence of microbes or lipids, glucose concentration, the tissue of origin, and the duration of the stimulus can change the direction of the effect.No directly conflicting evidence sufficiently relevant to demonstrate the absence of any link between hyperinsulinemia and pro-inflammatory activation of myeloid cells in humans has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the Evidence Review from the independent publications used to verify the steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on humans, animals, and cells	Describes a reciprocal relationship between macrophages, inflammation, insulin resistance, and hyperinsulinemia.	biologically consistent evidence	moderate
[1]	Cellular on primary human cells	Primary monocytes from healthy volunteers and adipose tissue from overweight individuals	Insulin increased lipopolysaccharide-induced pro-inflammatory reactivity and cell migration.	direct confirmation	moderate
[2]	Animal and cellular	Mice with myeloid deletion of Irs2 and macrophages	Hyperinsulinemia reduced IRS2 and impaired the IL-4-induced regulatory program.	direct confirmation	moderate
[3]	Genetic animal	Mice with insulin receptor deletion in myeloid cells	Loss of the receptor reduced high-fat diet-induced adipose inflammation and insulin resistance.	indirect confirmation	moderate
[4]	Human observational, animal, and cellular	36 human samples, mice, and 3T3-L1 adipocytes	Elevated insulin was associated with increased adipose inflammation and promoted it in experimental models.	indirect confirmation	moderate

[5]	Cellular and animal	Insulin-resistant murine macrophages and mice	Macrophage insulin resistance produced an M2-like phenotype and lower responses to lipopolysaccharide.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the narrative segment dedicated to macrophages as a meeting point between metabolism and inflammation. Independent evidence confirms that insulin can directly modify the function of monocytes and macrophages and that alterations in these signals can be associated with inflammation and insulin resistance in experimental models.

The framework is moderately supported, not definitive. The effect of insulin is not invariably pro-inflammatory: it depends on the cell type, the tissue, the presence of lipids or microbial stimuli, the glucose level, and the duration of exposure. Longitudinal and interventional studies in humans are needed to clarify when hyperinsulinemia acts as an initial factor, when as a consequence, and when as an amplifier of metabolic dysfunction.

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] **Insulin acutely activates metabolism of primary human monocytes and promotes a proinflammatory phenotype**
Ratter et al., 2021
Journal of Leukocyte Biology
DOI: https://doi.org/10.1002/JLB.3AB0120-019RR

[2] **Downregulation of macrophage Irs2 by hyperinsulinemia impairs IL-4-indeuced M2a-subtype macrophage activation in obesity**
Kubota et al., 2018
Nature Communications
DOI: https://doi.org/10.1038/s41467-018-07358-9

[3] **Myeloid Cell-Restricted Insulin Receptor Deficiency Protects Against Obesity-Induced Inflammation and Systemic Insulin Resistance**
Mauer et al., 2010
PLoS Genetics
DOI: https://doi.org/10.1371/journal.pgen.1000938

[4] **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

[5] **Insulin Resistance in Macrophages Alters Their Metabolism and Promotes an M2-Like Phenotype**
Ieronymaki et al., 2019
The Journal of Immunology
DOI: https://doi.org/10.4049/jimmunol.1800065