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Hyperinsulinemia in obesity, inflammation, and cancer - Evidence review

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1. ABSTRACT

The analyzed study is a narrative review examining the potential role of hyperinsulinemia—defined as insulin concentrations higher than those required to maintain normal glycemia—in obesity, inflammation, insulin resistance, and cancer. It does not present a single new experiment but integrates epidemiological, clinical, animal, and cellular data. The section relevant to "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi primarily concerns the hypothesis that persistently elevated insulin may actively contribute to metabolic inflammation and the progressive reduction of tissue response to the hormone.Available independent evidence shows that, in mice, increasing insulin while maintaining normal glycemia can increase inflammatory signals in adipose tissue; human immune cells exposed to insulin also exhibit more pro-inflammatory characteristics. A small physiological study in humans links peripheral hyperinsulinemia induced by insulin therapy to reduced muscle insulin sensitivity. However, longitudinal studies also indicate that, in some populations, increased adiposity may precede hyperinsulinemia. The book's narrative is therefore supported at a mechanistic level, but it does not demonstrate a single sequence valid for all people and all contexts.

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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 question addressed by the publication is whether hyperinsulinemia should be considered merely a compensatory response to reduced insulin efficacy or also a factor that can contribute to obesity, inflammation, insulin resistance, and tumor development. The central hypothesis is that persistent exposure to insulin can alter the behavior of metabolically active cells and immune cells, promoting self-reinforcing circuits.The reason for the citation in paragraphs 5.2 and 14.8 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is therefore precise. The review is used to frame a shift in perspective: hyperinsulinemia can precede, accompany, or exacerbate insulin resistance and can contribute to maintaining low-grade chronic inflammation.As it is a review, the study analyzed does not, on its own, demonstrate a universal causal relationship in humans. However, it can synthesize experiments in which insulin is directly modified and observational studies in which it is measured alongside other factors. The segment of the narrative most directly documented is this: a persistent excess of insulin signaling can activate intracellular pathways, including PI3K/AKT and MAPK/ERK, and promote inflammatory responses in tissues and immune cells.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the scientific literature, not an original experimental study or a systematic review with meta-analysis. The authors discuss human studies, mouse models, cell cultures, and genetic data related to insulin signaling, obesity, inflammation, aging, and cancer.No pre-registered literature search protocol is reported. There are no formal inclusion and exclusion criteria, databases searched, search dates, article selection procedures, standardized risk-of-bias assessments, or quantitative synthesis of the results. Consequently, the total number of sources included, the exact period covered by the research, and the aggregated quantitative endpoints are not reported in the available material.The authors primarily describe a biological chain: insulin binds to its receptor, activates signal transduction proteins, and can stimulate PI3K/AKT/mTOR and MAPK/ERK. In simple terms, these are systems through which the cell receives the message to use nutrients, grow, or modify its activity. If these signals remain active for too long, the effect can vary depending on the tissue, the dose, the duration of exposure, and the initial metabolic state.

4. RESULTS

The review reports that hyperinsulinemia can appear before hyperglycemia and, in some studies, before insulin resistance measured with specific techniques. It also describes experiments in which a genetic or pharmacological reduction of insulin secretion in rodents is associated with lower adiposity, less adipose tissue inflammation, and a better response to insulin. Since these results come from different studies, they do not constitute a single numerical estimate of the effect.For paragraph 5.2, the most relevant result is the indication that an experimental increase in insulin can promote the expression of pro-inflammatory mediators. The review cites data in which insulin infusion, while maintaining normal glycemia, increases circulating molecules in humans such as interleukin-6, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1. It also reports that lower insulin production in mice is accompanied by an adipose tissue gene expression profile less compatible with the activation of innate immunity.For paragraph 14.8, the relevant point is the possibility of a bidirectional relationship. The publication does not state that hyperinsulinemia always precedes insulin resistance. Instead, it acknowledges that insulin resistance can increase insulin secretion and that prolonged exposure to high insulin can, in turn, reduce tissue response. This cycle is biologically plausible, but its temporal sequence is not identical in all individuals.

5. INTERPRETATION

The main biological message is that insulin is not just a regulator of glycemia. When present in high amounts for prolonged periods, it can affect adipose tissue and immune system cells. In adipose tissue, this can increase the production of signals that recruit monocytes and macrophages, cells involved in both defense and inflammation. In monocytes and macrophages, insulin can alter energy use and the production of cytokines, which are immune signaling molecules.The proposed chain is: persistent

hyperinsulinemia activation of insulin signaling in adipose and immune cells increase in pro-inflammatory signals and recruitment of immune cells local worsening of the insulin response possible amplification of insulin resistance. The point that the publication subject to the Evidence Review supports most directly is the link between insulin signaling and the activation of potentially pro-inflammatory cellular pathways.This interpretation does not equate to proving that hyperinsulinemia is the sole cause of metabolic inflammation or type 2 diabetes. Excess fatty acids, increased adipose mass, genetic predisposition, reduced hepatic insulin clearance, a sedentary lifestyle, and impaired pancreatic beta-cell function can all contribute simultaneously. The strength of the narrative therefore depends on the convergence of studies that isolate, at least in part, the effect of insulin from other factors.

6. INDEPENDENT SUPPORTING EVIDENCE

An independent experiment provided direct confirmation of the passage regarding adipose tissue inflammation. Pedersen and colleagues studied diet-induced obese mice and genetically obese mice, reducing circulating insulin by approximately 50% through pharmacological interventions. The reduction in insulin was associated with a lower macrophage content and lower expression of inflammatory mediators in adipose tissue, with an improvement in the insulin response without changes in body weight in some comparisons. Conversely, insulin infusion in lean, euglycemic mice increased the expression of cytokines in adipose tissue. In 3T3-L1 adipocytes, insulin increased CCL2 messenger RNA approximately tenfold within six hours; this effect was blocked by the inhibition of ERK, a protein in the MAPK pathway. The study also included an association in humans: in 36 people with obesity, higher insulin was associated with greater inflammatory markers in adipose tissue, independently of body mass index. However, the causal link remains demonstrated primarily in mice and cells [1].Ratter and colleagues verified a complementary part of the chain in human immune cells. In primary monocytes—that is, macrophage precursors obtained from blood—acute exposure to insulin activated PI3K/AKT/mTOR, increased glycolysis and oxygen consumption, and increased interleukin-6 secretion after stimulation with lipopolysaccharide. After 24 hours of insulin exposure, the monocytes showed an increase in lipopolysaccharide-induced TNF-alpha production and greater migration toward MCP-1. In a sample of overweight individuals, the number of macrophages in adipose tissue was positively correlated with plasma insulin. These results support the premise that insulin can directly modulate immune activity, but experimental concentrations and ex vivo exposure do not entirely reproduce the physiology of chronic hyperinsulinemia in humans [2].For paragraph 14.8, Gregory and colleagues compared three groups of ten participants: healthy controls, people with GCK-MODY monogenic diabetes, and people with type 1 diabetes. Subjects with type 1 diabetes had basal insulinemia approximately 2.5 times higher than the other two groups, while glycated hemoglobin was similar to that of the GCK-MODY group. During the hyperinsulinemic-euglycemic clamp—a technique that measures tissue response to insulin while maintaining stable glycemia—the stimulation of muscle glucose utilization was 22% to 29% less effective in type 1 diabetes. In the statistical model, insulinemia, but not glycemia, was associated with muscle insulin sensitivity. The study reinforces the idea that high peripheral insulinemia may contribute to insulin resistance; however, it cannot be automatically transferred to type 2 diabetes, as it compares different clinical conditions and includes a very small sample [3].

7. CONFLICTING EVIDENCE

Significant evidence conflicting with a unique sequence in which hyperinsulinemia always precedes increased adiposity comes from the Bogalusa Heart Study. In 948 participants followed from childhood to adulthood, the temporal association between body mass index and fasting insulin primarily ran from increased body mass index to increased insulin, not the other way around. The coefficient for body mass index insulin was 0.326 with $P < 0.001$, while the coefficient for insulin body mass index was -0.023 with $P = 0.207$. This does not refute experiments in which insulin influences inflammation or insulin sensitivity; however, it shows that, during childhood in this cohort, adiposity more clearly preceded hyperinsulinemia [4].The result highlights an essential

limitation: obesity, hyperinsulinemia, inflammation, and insulin resistance can form a reciprocal circuit, but they do not necessarily start at the same point. Furthermore, a single fasting insulin value does not distinguish between increased pancreatic secretion and reduced hepatic insulin clearance. For this reason, it is incorrect to interpret every association between elevated insulin and inflammation as proof that insulin is the sole initial cause of the process.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to evaluate specific passages of the book's 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	Integrates evidence that hyperinsulinemia may contribute to inflammation and insulin resistance.	biologically consistent evidence	moderate
[1]	Animal, cellular, and observational	Obese or lean mice, 3T3-L1 adipocytes, and 36 people with obesity	Reducing insulin attenuated adipose inflammation in mice; infusing it increased it in lean mice.	direct confirmation	moderate
[2]	Human cellular and ex vivo	Primary human monocytes; subgroups subjected to clamp	Insulin increased metabolic signals and certain pro-inflammatory responses in monocytes.	indirect confirmation	moderate
[3]	Comparative clinical physiological study	30 participants, ten per group	In type 2 diabetes with higher insulinemia, muscle insulin sensitivity was reduced.	indirect confirmation	moderate
[4]	Longitudinal observational	948 participants followed from childhood to adulthood	Increased body mass index preceded the increase in fasting insulin during childhood.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the idea that hyperinsulinemia may have biological effects beyond the control of glycemia. Independent evidence confirms that elevated insulin can increase inflammatory activation of adipose tissue in experimental models and modify certain functions of human immune cells. The link with insulin resistance is supported, but it depends on the clinical context and does not define a universal sequence.The book's narrative is therefore confirmed primarily at a mechanistic level: hyperinsulinemia, inflammation, and insulin resistance can fuel one another. Broader validation in humans remains necessary, with longitudinal and experimental studies capable of distinguishing the effect of insulin from that of adiposity, diet, reduced hepatic insulin clearance, and other metabolic alterations.

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.

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