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Molecular mechanisms of glucocorticoid-induced insulin resistance - Evidence review

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1. ABSTRACT

The analyzed study is a narrative review of the mechanisms by which an excess of glucocorticoids—hormones involved in the stress response and used as anti-inflammatory drugs—can promote insulin resistance. The authors integrate data from humans, animals, and cell cultures, describing a reduced efficacy of insulin signaling, particularly in muscle, liver, and adipose tissue. The most relevant finding concerns the reduction in the activity of the IRS-1, PI3K, and AKT sequence, which is necessary for cells to absorb and utilize glucose.In "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, this publication contributes to the narrative that chronic exposure to cortisol can compromise the peripheral response to insulin. Independent studies confirm a reduction in insulin sensitivity in humans following prednisone administration and show consistent alterations of IRS-1 and AKT in adipose and muscle cells. However, some results in human subcutaneous adipose tissue indicate opposite responses depending on the specific area studied. The confirmation is therefore primarily mechanistic, with clinical support for the systemic effect.

ONLINE ARTICLE

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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 how glucocorticoids can reduce insulin sensitivity, meaning they make a greater amount of the hormone necessary to achieve the same glucose uptake into cells. The hypothesis examined is that a prolonged excess of these hormones interferes with insulin signaling in multiple organs, contributing to an increase in glycemia and, over time, to metabolic disorders.The relevance to section 4.14 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns, above all, the segment of the chain that goes from persistent exposure to glucocorticoids to the reduced activity of IRS-1, PI3K, and AKT. IRS-1 is a protein that transmits the message received from the insulin receptor into the cell; PI3K and AKT are subsequent steps that facilitate, among other things, the transport of glucose into cells.As a narrative review, the publication does not by itself demonstrate a new causal relationship in a single population. Instead, it brings together previous studies and describes how results differ according to organ, species, dose, and duration of exposure. It can therefore support a plausible biological explanation, but it cannot establish that psychological stress itself causes diabetes in every person.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review, not a clinical study with participants recruited directly by the authors. The available material describes the integration of previous studies conducted in humans, rodents, isolated tissues, and cell cultures. The focus is on the effects of natural glucocorticoids, such as cortisol and corticosterone, and synthetic ones, primarily dexamethasone and prednisone.The authors organize the evidence by insulin target organ: adipose tissue, liver, skeletal muscle, pancreas, intestine, bone, and brain. Experiments are described that measured glucose uptake, hepatic glucose production, phosphorylation of insulin signaling proteins, and changes in gene expression. Phosphorylation is the addition of a small chemical group to a protein, a process that often modifies its activity.A detailed literature search strategy, formal inclusion and exclusion criteria for studies, systematic assessment of the risk of bias, and meta-analysis are not reported in the available material. Therefore, an overall sample size, a single primary endpoint, or a follow-up typical of a review are not available.

4. RESULTS

The central finding of the review is that an excess of glucocorticoids can reduce insulin action in tissues essential for the control of glycemia. In simple terms, muscle and adipose tissue become less efficient at absorbing glucose, while the liver tends to produce more of it. The overall result can be an increase in glycemia and a greater demand for insulin.In skeletal muscle, the publication reports that glucocorticoids reduce the translocation of GLUT4, the transporter that carries glucose from the blood into the cell. It also describes a reduction in PI3K activity and AKT phosphorylation in cellular and animal studies. These changes are consistent with lower insulin-stimulated glucose uptake.In adipose tissue, dexamethasone is associated with lower glucose uptake and a reduction in IRS-1, PI3K, and AKT in rat adipocytes. The review also notes increased lipolysis, meaning a greater release of fatty acids from adipose stores. Excess fatty acids can accumulate in other organs and contribute to their metabolic dysfunction.In the liver, the publication describes an increase in the expression of PEPCK and G6Pase, enzymes that promote glucose production. The proposed mechanism includes lower AKT activation, less inhibition of FOXO1, and greater activity of gluconeogenesis genes—that is, the production of glucose from non-sugar substances. However, the review emphasizes that much of the molecular evidence is derived from animal and cellular models.The passage most directly linked to the book's narrative is therefore the sequence: elevated glucocorticoids alteration of IRS-1/PI3K/AKT reduced glucose entry into muscle and adipose cells. The review does not attribute the same effect, with the same intensity, to every tissue or every experimental condition.

5. INTERPRETATION

The biological significance is that cortisol and glucocorticoid medications can help the body rapidly make energy available during an acute situation, but prolonged stimulation can become metabolically unfavorable. When insulin signaling is less effective,

glucose remains in the blood more easily instead of being properly utilized or stored.The publication subject to the Evidence Review places this phenomenon along a plausible chain. The insulin receptor activates IRS-1; IRS-1 promotes the activation of PI3K; PI3K contributes to the activation of AKT; AKT promotes processes such as the translocation of GLUT4 to the cell membrane. If one or more of these steps are reduced, the muscle or adipose cell may absorb less glucose.The data strongly support the existence of molecular alterations induced by glucocorticoids in specific experimental models. However, they do not prove that any increase in cortisol due to daily stress inevitably produces the same cascade in humans. The response depends on the duration of exposure, hormone concentration, individual predisposition, and the tissue involved.

6. INDEPENDENT CONFIRMING EVIDENCE

Clinical confirmation of the systemic effect comes from a randomized study conducted on healthy, normal-weight men. After one week of prednisone, 25 mg per day reduced by 35% the amount of glucose eliminated by the body during the first phase of the hyperinsulinemic-euglycemic clamp, a test that measures how effectively insulin promotes glucose utilization. In the second phase, both 25 mg and 10 mg reduced glucose availability by 33% and 15%, respectively, compared to the placebo. This study confirms in humans that even short-term exposure to pharmacological glucocorticoids can reduce insulin sensitivity, but it does not directly identify all the molecular steps within the cells [1].In adipose tissue, Burén and colleagues studied primary rat adipocytes exposed to dexamethasone for 24 hours. The drug reduced basal and insulin-stimulated uptake by 40–50%. In parallel, IRS-1 decreased by approximately 75%, PI3K by about 20%, the amount of AKT, also known as PKB, by about 45%, and insulin-induced AKT phosphorylation by about 40%. This experiment directly confirms the molecular segment described in the book for adipose cells, but the model is animal-based and isolated from the whole organism [2].In muscle, Morgan and colleagues combined human and rodent myotube cultures, muscle fragments, and mouse models. Dexamethasone reduced insulin-stimulated glucose entry, decreased IRS-1 messenger RNA and protein, and increased the inactivating phosphorylation of IRS-1 at the Ser307 position. In mice, the inhibition of 11β-HSD1, an enzyme that regenerates active glucocorticoids in tissues, was associated with lower fasting glycemia, less inactivated IRS-1, and greater AKT phosphorylation. Research therefore reinforces the link between glucocorticoids, IRS-1, and AKT in muscle, with predominantly experimental evidence [3].These findings are convergent because they analyze different levels of the same narrative: the effect on the whole organism in humans, the molecular defect in adipocytes, and the molecular-muscular defect with verification in animals. None of these studies, in isolation, demonstrates all the long-term clinical consequences of endogenous cortisol hyperactivation.

7. CONFLICTING EVIDENCE

A relevant and directly pertinent finding shows that the response to glucocorticoids is not uniform across all fat depots. In a human subcutaneous adipocyte cell line, dexamethasone administered for 24 hours or seven days increased insulin-stimulated phosphorylation of IRS-1 and AKT, a signal consistent with increased cellular insulin sensitivity. This effect was also observed in the presence of high insulin concentrations [4].This evidence does not negate the reduction in whole-body insulin sensitivity observed after glucocorticoid administration. Rather, it indicates that subcutaneous adipose tissue may respond differently than muscle, visceral adipose tissue, or the organism as a whole. The main limitation is the use of a cell line, which does not replicate the interactions with the liver, muscle, inflammation, blood flow, and endocrine system present in a person.The discrepancy therefore requires caution when describing cortisol as an identical inhibitor of the IRS-1/PI3K/AKT pathway in all adipose cells. No directly conflicting evidence sufficiently pertinent to the reduction of systemic insulin sensitivity induced by glucocorticoids has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent research. The strength of the evidence considers relevance, experimental model, and the possibility of extending the results to humans.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Human, animal, and cell studies	Summarizes glucocorticoid-induced alterations in IRS-1/PI3K/AKT signaling and glucose metabolism.	biologically consistent evidence	moderate
[1]	RCT	Healthy, normal-weight men treated for one week with prednisone or placebo	Prednisone reduced insulin sensitivity in a dose-dependent manner.	direct confirmation	moderate
[2]	Cellular	Primary rat adipocytes	Dexamethasone reduced glucose uptake, IRS-1, PI3K, AKT, and AKT phosphorylation.	direct confirmation	moderate
[3]	Cellular and animal	Human and murine myotubes, muscle fragments, and mice	Glucocorticoids reduced IRS-1 and glucose uptake; 11β-HSD1 inhibition increased active AKT.	direct confirmation	moderate
[4]	Cellular	Differentiated human subcutaneous adipocyte line	Dexamethasone increased insulin-stimulated phosphorylation of IRS-1 and AKT.	discordant evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the section of the book linking prolonged excess of glucocorticoids to reduced peripheral insulin signaling efficacy. Independent evidence confirms that prednisone can reduce insulin sensitivity in humans and that dexamethasone and related glucocorticoids can alter IRS-1 and AKT in experimental models.The confirmation is more robust for the general phenomenon of glucocorticoid-induced insulin resistance than for a single molecular sequence valid across all organs. The differences observed in adipose tissue indicate that the mechanism is dependent on the biological context. Direct extrapolation from pharmacological glucocorticoids to chronic psychological stress requires further validation in humans.

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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