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ORIGINAL RESEARCH

An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects - A review of the evidence

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The original study evaluated whether seven days of prednisone could reduce insulin sensitivity in healthy individuals and which biological step was most involved. Ten normal-weight adults underwent hyperinsulinemic-euglycemic clamp tests, a technique that measures how much glucose the body can utilize while blood glucose levels are kept stable. A separate group of human fat cells was analyzed in the laboratory.Prednisone increased fasting glycemia and insulin and reduced insulin-induced glucose utilization. In fat cells, no significant difference emerged in insulin binding to the receptor, while glucose transport decreased. Within the narrative framework of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes primarily to the description of acute glucocorticoid-induced insulin resistance, rather than the direct demonstration of lower insulin receptor or IRS-1 expression. Independent studies confirm the worsening of insulin sensitivity and indicate possible alterations of IRS-1 in muscle; however, other cellular data show that the defect may be localized primarily in glucose transport. The most prudent conclusion is therefore that the metabolic effect is well-documented, while the precise level of the insulin cascade depends on the tissue and the model studied.

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 whether prednisone, a glucocorticoid used as an anti-inflammatory drug, induces a reduced response to insulin in healthy individuals through an insulin receptor defect or through a subsequent step inside the cell. The authors' hypothesis was that the drug could decrease the ability of insulin to promote the entry and utilization of glucose in tissues.The relevance of the study stems from the fact that insulin does not act solely by lowering glycemia. After binding to its receptor, it initiates intracellular signals that primarily allow muscle and adipose tissue to utilize glucose. If these tissues respond less effectively, the pancreas tends to produce more insulin, and glycemia may increase.In Chapter 4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication is cited in three contexts: the initial insulin receptor signal, the role of IRS-1 and IRS-2 proteins, and the insulin resistance observable after brief exposure to prednisone. The most directly relevant finding is the latter: prednisone induced systemic insulin resistance in clinically healthy subjects. However, the study cannot demonstrate a reduction in receptor expression in muscle or liver, because the available material describes insulin binding only in isolated adipocytes and does not report measurements of receptor expression in muscle and liver tissues. It also cannot demonstrate a reduction in IRS-1 or its phosphorylation, as these variables are not reported in the available material.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available text is only the abstract; information not contained in the abstract is therefore not included in the available material. The human study involved 10 healthy, normal-weight subjects with a mean age of 35 ± 7 years. Each participant received prednisone, 15 mg twice daily, or a placebo—a treatment lacking the active ingredient—for seven days. The sequence was randomized, meaning it was assigned by chance, and the two phases were separated by approximately one month.Before and during a hyperinsulinemic-euglycemic clamp, tritium-labeled glucose was infused, a substance that allows for tracking glucose fluxes within the body. The clamp was repeated at three stable insulin concentrations: approximately 100, 1,000, and 10,000 microU/ml. In simple terms, this method allows researchers to verify whether the body is able to utilize glucose when low, medium, or high levels of insulin are present.The authors measured fasting glycemia and insulin, endogenous glucose production, and the insulin sensitivity index, expressed as the metabolic clearance rate of glucose. In a separate in vitro experiment—that is, outside the body—they analyzed adipocytes obtained from 16 normal-weight surgical candidates with a mean age of 40 ± 8 years. Ten had been treated with a placebo and six with prednisone according to the same regimen. Specific insulin binding and the cellular transport of 3-O-methyl-glucose, a molecule used to estimate glucose entry into the cell, were evaluated. Full inclusion and exclusion criteria, the sex of the participants, the randomization method, and further statistical details are not reported in the available material.

4. RESULTS

Prednisone worsened the metabolic response to insulin. After treatment, fasting glycemia was higher compared to placebo, 89.5 ± 2.1 versus 83.7 ± 1.9 mg/dl, and fasting insulin was also higher, 17.8 ± 1.2 versus 14.3 ± 0.8 microU/ml; for both differences, the P-value was less than 0.01. In other words, even in healthy subjects, after one week of prednisone, more insulin was required in the presence of higher glycemia.The most marked reduction concerned peripheral glucose utilization. The insulin sensitivity index, i.e., the amount of glucose removed from the blood in relation to body weight and time, was lower after prednisone at all insulin concentrations studied. At approximately 100 microU/ml, it was 2.8 ± 0.3 versus 7.4 ± 1.1 ml/kg/min; at approximately 1,000 microU/ml, it was 6.0 ± 0.5 versus 12.2 ± 1.1 ml/kg/min; at approximately 10,000 microU/ml, it was 7.4 ± 0.6 versus 14.4 ± 0.5 ml/kg/min. All these differences had a P-value of less than 0.001, and were therefore unlikely to be due to random variation.Fasting glucose production by the body, largely attributable to the liver, was higher after prednisone: 3.7 ± 0.2 versus 2.9 ± 0.2 mg/kg/min, with a P-value of less than 0.001. However, according to the authors' interpretation, the observed insulin resistance was primarily due to reduced peripheral glucose utilization. During the clamp with approximately 100

microU/ml of insulin, the suppression of glucose production was less pronounced after prednisone, but the difference was not statistically significant. At higher insulin concentrations, suppression was complete both after prednisone and after placebo.In adipose cells, specific insulin binding was not significantly different between prednisone and placebo. This is an important finding for interpreting sections 4.1 and 4.2 of the book: in the cellular model analyzed, the drug did not demonstrate a reduction in insulin binding to the receptor. Glucose transport, however, decreased after prednisone both under basal conditions, 0.40 ± 0.10 versus 0.54 ± 0.12 pmol per 100,000 cells, and at maximum insulin stimulation, 0.59 ± 0.04 versus 0.92 ± 0.12 pmol per 100,000 cells. The differences were associated with P-values of less than 0.05 and less than 0.005, respectively.

5. INTERPRETATION

The main biological message is that prednisone can make tissues less capable of using glucose, even in people without diabetes. In the model studied, the problem did not appear primarily as an inability of insulin to bind to the fat cell. Instead, a subsequent defect emerged: after the initial signal, glucose was transported into the cell less effectively.This distinguishes two levels of the insulin cascade. The first is the insulin receptor, the membrane protein that recognizes the hormone. The second includes post-receptor steps, i.e., the intracellular mechanisms that transform that signal into glucose uptake. The study analyzed places the defect primarily at the second level, because insulin binding to adipocytes did not change significantly, while glucose transport decreased.The publication is therefore consistent with the passage in paragraph 4.14 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which describes systemic insulin resistance after short exposures to prednisone. The correspondence with the sentences in paragraphs 4.1 and 4.2 is more limited. The work does not measure insulin receptor expression in muscle and liver and does not analyze IRS-1. The statement that prednisone would directly reduce the expression of the receptor or IRS-1 is therefore not documented by this specific study.The main limitation is the small sample size: 10 subjects for the clinical part and 16 for the experiment on adipocytes. Furthermore, the duration was only seven days, and the participants were healthy and of normal weight. The results show an acute effect of the drug in this context, but they do not automatically define what happens after longer therapies, in elderly people, or in those with obesity, diabetes, or inflammatory diseases.

6. INDEPENDENT CONFIRMATORY EVIDENCE

The most direct confirmation of the claim that short-term exposure to prednisone can induce insulin resistance in healthy subjects comes from a randomized study conducted on lean, healthy men. After one week, 25 mg of prednisone per day reduced whole-body glucose utilization by 35% during the first phase of the clamp and by 33% during the second phase compared to the placebo. Even 10 mg per day reduced glucose utilization by 15% in the second phase. The study therefore confirms the direction of the effect observed in the analyzed publication and shows a dose-response relationship. The limitation is that the sample included only healthy men and that the work was not designed to establish which intracellular protein produced the defect [1].Regarding the section of the book concerning IRS-1, an experimental study examined human myotubes, rodent myotubes, muscle fragments, and mouse models. Dexamethasone, another glucocorticoid, reduced insulin-stimulated glucose uptake and decreased both the messenger RNA and the amount of IRS-1 protein. It also increased the phosphorylation of IRS-1 at serine 307, a modification associated with reduced insulin signaling efficacy. In mice, inhibition of the 11β-HSD1 enzyme reduced this inactivating modification of IRS-1 and improved insulin sensitivity. This research provides mechanistic support for the idea that excess glucocorticoid activity may involve IRS-1 in muscle, but it does not prove that prednisone produced the same effect in the participants of the original study [2].Overall, independent evidence outlines a plausible sequence: pharmacological glucocorticoid reduced tissue insulin response reduced glucose utilization. The involvement of IRS-1 is supported primarily by cellular and animal models, while direct demonstration in humans for prednisone and for each specific tissue remains more limited.

7. CONFLICTING EVIDENCE

An experiment on 3T3-L1 adipocytes, murine cells commonly used to study adipose tissue, has highlighted a scenario that calls for caution in assuming the defect always lies at the same point in the insulin signaling cascade. After dexamethasone treatment, the expression of GLUT1, a basal glucose transporter, decreased by 30%; furthermore, the overall amount of GLUT4 did not change, but its translocation to the membrane in response to insulin was reduced. GLUT4 is the transporter that allows glucose to enter the cell when the insulin signal is received.In the same model, insulin receptor phosphorylation was not altered by dexamethasone. The authors therefore attributed the insulin resistance primarily to a defect in glucose transport and GLUT4 translocation, rather than an initial blockage of the receptor signal [3]. This result is consistent with the original study regarding the reduction in glucose transport, but it limits the interpretation that glucocorticoids must necessarily reduce the insulin receptor or impair its binding.This discrepancy does not deny that different glucocorticoids may influence IRS-1 or other intracellular signals in certain tissues. However, it shows that the mechanism may depend on the type of glucocorticoid, the dose, the duration of exposure, and the biological model. 3T3-L1 cells are not human adipose tissue in vivo; therefore, this evidence defines an interpretative limit, not a definitive clinical conclusion.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the results observed in the original study from the independent publications used to confirm or contextualize the specific narrative passage of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Randomized crossover study in humans and in vitro cell study	10 healthy normal-weight adults; adipocytes from 16 surgical candidates	Seven days of prednisone reduced peripheral glucose utilization; insulin binding in adipocytes did not change significantly, while glucose transport decreased.	direct confirmation	moderate
[1]	RCT with euglycemic-hyperinsulinemic clamp	Healthy, lean men; sample size not reported in the available abstract	One week of prednisone reduced whole-body glucose utilization in a dose-dependent manner compared to placebo.	direct confirmation	moderate
[2]	Cellular, explant, and animal study	Human and murine myotubes, muscle explants, and mice	Dexamethasone reduced insulin-stimulated glucose uptake, reduced IRS-1, and increased an inactivating phosphorylation of IRS-1.	biologically consistent evidence	preliminary

[3]	Cellular study	Murine 3T3-L1 adipocytes	Dexamethasone reduced glucose transport and GLUT4 translocation without altering insulin receptor phosphorylation.	discordant evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study shows that seven days of prednisone can reduce insulin sensitivity in healthy adults, primarily by decreasing peripheral glucose utilization. This finding is well-supported by independent clinical research using the euglycemic-hyperinsulinemic clamp technique.However, the publication does not demonstrate a reduction in insulin receptor expression in the muscle or liver, nor a reduction in IRS-1 in the studied participants. Its cellular data points in a different direction: insulin binding to adipocytes was not significantly reduced, while glucose transport decreased. The involvement of IRS-1 remains mechanistically supported by other models, but requires direct validation in humans for the specific prednisone dosage, duration, and tissue.

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.

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