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Effect of sustained physiological hyperinsulinemia and hyperglycemia on insulin secretion and insulin sensitivity in humans - A review of the evidence

Dr.ssa M. Bitonti[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether a physiological yet prolonged increase in blood insulin can alter the body's response to the hormone in healthy young adults. In 15 participants, 72–96 hour insulin or glucose infusions were followed by metabolic clamps, experimental techniques that allow for the measurement of how much glucose the body uses when insulin is maintained at controlled levels.During hyperinsulinemia with normal glycemia, systemic glucose utilization decreased by 20–40%, primarily due to a reduction in the amount destined for glycogen synthesis. This result contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which suggests that a persistent excess of insulin may contribute to the maintenance of insulin resistance. Independent studies in humans have replicated the glycogen synthesis defect, and cellular studies have documented a weakening of intracellular insulin signaling. However, a small study with concurrent hyperglycemia and hyperinsulinemia observed an increase, rather than a reduction, in insulin sensitivity. Overall, the hypothesis is well-supported experimentally, but its long-term clinical relevance requires caution.

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MISSION

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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.

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 moderately elevated insulin concentrations, maintained for several days, could reduce insulin sensitivity even in young, healthy individuals. This hypothesis was significant because hyperinsulinemia—that is, an amount of insulin in the blood higher than usual relative to glycemia—is often interpreted as a compensatory consequence of insulin resistance. The study also tested the inverse hypothesis: that persistent exposure to insulin may contribute to producing a reduced response to the hormone.The relevance to paragraph 3.5 is precise. The publication provides a human experiment in which insulin was artificially increased while maintaining normal glycemia; after this exposure, the amount of glucose utilized under insulin stimulation decreased. The study therefore documents a segment of the book's narrative: prolonged hyperinsulinemia reduced peripheral response to insulin.However, it does not prove that every person with elevated insulin will develop insulin resistance, nor does it establish what the effects are after months or years. It also does not directly prove that the defect is localized in the muscle, because no muscle biopsies are reported in the available material. The prevalence of the defect in the non-oxidative pathway nonetheless makes skeletal muscle involvement biologically plausible, as it is a major site for glycogen storage.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study involved a total of 15 healthy young subjects. This information is not reported in the available material for either of the two protocols, nor are sex, mean age, body mass index, inclusion or exclusion criteria, recruitment period, or methods of assignment to the protocols provided.In the first protocol, participants received an insulin infusion for 72–96 hours that increased insulinemia by 72 pmol/L, while maintaining normal glycemia. In the second protocol, a glucose infusion increased glycemia by 1.4 mmol/L and insulinemia by 78 pmol/L for 72 hours. Before and after the infusions, a three-level hyperinsulinemic-euglycemic clamp and a hyperglycemic clamp were performed.The hyperinsulinemic-euglycemic clamp maintains stable glycemia while insulin is infused at defined rates; the amount of glucose required to prevent glycemia from dropping allows for the estimation of tissue response to insulin. In the hyperglycemic clamp, glycemia is maintained at 6.9 mmol/L to evaluate glucose-induced insulin secretion. The authors also distinguished between glucose oxidized to produce energy and non-oxidized glucose, which is primarily destined for glycogen synthesis. The specific method used for this distinction is not reported in the available material.

4. RESULTS

After four days of hyperinsulinemia with normal glycemia, overall glucose disposal in the body decreased by 20–40% compared to the initial assessment. In simple terms, for the same insulin stimulus, the tissues used less glucose. The defect was attributed to a reduction in non-oxidative glucose disposal, i.e., the portion primarily used to build glycogen, an energy reserve. The reduction in this component was significant at every stage of the insulin clamp, with $p<0.01$.Insulin continued to suppress glucose production by the liver. This indicates that, under the experimental conditions considered, no reduction in the hepatic response to insulin was observed. The alteration detected therefore primarily concerned peripheral glucose management. Furthermore, after insulin infusion, the ability of acute hyperglycemia to stimulate insulin secretion was significantly reduced. The numerical extent of this decrease is not reported in the available material.In the glucose protocol, where both glycemia and insulinemia were elevated, overall glucose disposal did not change. However, glucose oxidation increased, while non-oxidative disposal decreased by 25–39%, with $p<0.01$. In this same protocol, the plasma insulin response to a subsequent acute increase in glycemia more than doubled. Here, too, the suppression of hepatic glucose production by insulin did not change.The result most consistent with the contents of the book is therefore more targeted: prolonged exposure to elevated insulin was followed by reduced insulin action on glucose storage in the form of glycogen, without a measurable defect in the hepatic suppression of glucose production.

5. INTERPRETATION

The primary biological significance is that the body may become less efficient at storing glucose as a reserve when exposed to excess insulin for days, even if glycemia remains normal. Glycogen is the form in which the body stores glucose, primarily in the muscles and liver; a reduction in its synthesis can contribute to keeping more glucose in circulation after meals.This finding does not indicate that insulin is inherently harmful or that hyperinsulinemia is the sole cause of insulin resistance. Instead, it shows a specific experimental causal relationship: in healthy subjects, a prolonged increase in insulin precedes a measurable reduction in insulin response. The use of a protocol where glycemia is maintained at normal levels is essential, as it limits the possibility of attributing the result exclusively to hyperglycemia.The publication subject to this Evidence Review therefore supports the initial part of the circuit described in the book: a persistent increase in insulin can promote tissue desensitization. It does not directly document all the molecular steps mentioned in the paragraph, such as reduced phosphorylation of the receptor, IRS-1, or AKT. Nor does it allow for the conclusion that the same experimental effect, observed over a few days, alone explains the clinical development of type 2 diabetes.

6. INDEPENDENT SUPPORTING EVIDENCE

Confirmation in humans has come from a previous experimental study, in which a 20-hour insulin infusion, compared with a saline solution, significantly reduced insulin sensitivity after the infusion was stopped. Since the authors controlled glycemia and assessed glucose disposal using a clamp and minimal model, the result confirms the step whereby hyperinsulinemia can precede and promote a reduced response to insulin. The limitation is that the sample size and exposure were brief, and the publication does not establish long-term effects [1].A second experimental study investigated the specific step most relevant to this paragraph: glycogen synthesis. Twenty healthy adults received a low-dose insulin infusion for 24 or 72 hours. After exposure, insulin was less effective at increasing both non-oxidative glucose disposal and the activity of glycogen synthase, the enzyme that allows glucose to be converted into glycogen. The reduction in non-oxidative disposal was 34% after 24 hours and 58% after 72 hours. This is a direct and biologically more detailed confirmation of the alteration described in the original study [2].A cellular model provided a possible molecular link. Primary muscle cells obtained from healthy donors and maintained for three days with insulin showed a reduction in glucose uptake after subsequent insulin stimulation. There was also a reduction in the phosphorylation of IRS-1 and AKT, the steps by which the insulin signal is transmitted from the cell surface to the mechanisms that regulate glucose use. This study confirms at the cellular level that prolonged exposure to insulin can weaken the response to subsequent exposure, but it cannot replace evidence in the human body [3].Taken together, these studies build a coherent chain: persistently elevated insulin can be followed by lower insulin sensitivity in humans; the defect particularly affects glycogen formation; and in muscle cells chronically exposed to insulin, a weakening of intracellular signals essential for glucose uptake is also observed. They do not prove that this circuit is identical in all tissues or in all people with type 2 diabetes.

7. CONFLICTING EVIDENCE

There is data suggesting that the effect of hyperinsulinemia should not be interpreted as uniform. In a small study of six healthy men, a 24-hour glucose infusion resulted in both mild hyperglycemia and hyperinsulinemia. Instead of decreasing, the insulin sensitivity index increased from 4.8 to 8.2 × 10–5 min–1·pmol–1, with $p<0.05$. The insulin response to glucose also increased. This result is the opposite of that observed following isolated hyperinsulinemia [4].However, this divergence can be interpreted within the experimental context. The conflicting study combined increased glucose and insulin, had a shorter duration, and used a different method to estimate insulin action. It does not directly refute the result of the analyzed study, in which glycemia was maintained at normal levels during insulin exposure. Rather, it shows that the response depends on the duration, the level of glycemia, the experimental pathway, and the measure used to assess insulin sensitivity.No directly conflicting evidence has been identified that is sufficiently relevant to exactly replicate a 72–96 hour exposure to physiological hyperinsulinemia under

euglycemic conditions and show the absence of a peripheral defect; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Human physiological experimental	15 healthy young subjects	After 72–96 hours of hyperinsulinemia, glucose disposal decreased by 20–40%, primarily in the non-oxidative component.	direct confirmation	moderate
[1]	Human physiological experimental	Healthy adults; sample size not reported in the consulted material	After 20 hours of insulin infusion, insulin sensitivity decreased significantly compared to baseline and saline control.	direct confirmation	moderate
[2]	Human physiological experimental	20 healthy adults	Hyperinsulinemia for 24–72 hours reduced non-oxidative glucose disposal and glycogen synthase activation.	direct confirmation	moderate
[3]	Cellular	Primary human muscle cells from healthy donors	Three days of insulin exposure reduced glucose uptake and phosphorylation of IRS-1 and AKT following re-stimulation.	biologically consistent evidence	preliminary
[4]	Human physiological experimental	Six healthy men	Twenty-four hours of concurrent hyperglycemia and hyperinsulinemia increased the insulin sensitivity index.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that a few days of physiological hyperinsulinemia, maintained with normal glycemia, can reduce the peripheral response to insulin in healthy young adults. The observed defect primarily concerns the storage of glucose as glycogen, while the measured hepatic response remained preserved.Independent confirmations in humans make the idea that hyperinsulinemia can contribute to, as well as result from, insulin resistance quite well-supported. Cellular data make a weakening of insulin signaling in the muscle plausible. However, the evidence does not allow this result to be transformed into a single explanation for diabetes or a general therapeutic conclusion. The mechanism appears to be dependent on the duration of exposure and the metabolic context.

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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