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ORIGINAL RESEARCH

Nutrient and non-nutrient regulators of insulin secretion - A review of the evidence

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1. ABSTRACT

The analyzed study is a narrative review examining the numerous signals capable of regulating insulin secretion by pancreatic beta cells. Its central message is that glucose represents the primary physiological stimulus, but not the only one: amino acids, fatty acids, other energy substrates, and non-nutritional factors can modify the basal and post-meal insulin response.In paragraph 2.1.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication helps support the idea that the postprandial insulin response derives from the integration of multiple signals, sometimes even beyond glucose concentration alone. Independent studies in humans confirm the role of intestinal incretins and fatty acids; experimental data on human pancreatic islets support the contribution of specific amino acids. However, a meta-analysis does not detect consistent acute effects of low-energy sweeteners on insulin. The narrative is therefore well-supported for nutrients and intestinal signals, but requires caution when extended indiscriminately to all additives or non-nutritional factors.

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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 question addressed by the publication is how pancreatic beta cells, the cells that produce insulin, integrate signals from glucose and other stimuli to adapt insulin secretion to the body's needs. The general hypothesis is that secretion is not regulated by a single nutrient, but by a network that includes amino acids, fatty acids, intestinal signals, metabolic status, biological rhythms, and environmental factors.This perspective is relevant to paragraph 2.1.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because the cited passage states that the insulin response after a meal does not depend exclusively on glycemia. The publication subject to this evidence review strongly supports this segment of the narrative: multiple metabolic and non-metabolic stimuli can converge on beta cells and modify the quantity, timing, and dynamics of insulin release.As this is a review, the study does not directly compare groups of participants nor does it demonstrate a unique causal relationship between each cited factor and hyperinsulinemia. Furthermore, only the abstract is available. Therefore, the bibliographic research procedures, study selection criteria, and formal quality assessment are not reported in the available material.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a review of scientific literature, not an original experimental study on a new cohort of people or animals. The abstract indicates that the authors integrated evidence from preclinical models and human *in vitro* systems, meaning studies conducted on cells or tissues outside of a living organism.The topics examined include the role of glucose, amino acids, fatty acids, alternative fuels, and non-nutritional factors in insulin secretion. Also discussed are the functional stress of beta cells, reactive oxygen species, changes in beta-cell mass and function throughout life, circadian and pulsatile secretion rhythms, as well as genetic, environmental, pharmacological, and lifestyle-related influences.The search strategy, databases consulted, search period, inclusion and exclusion criteria, number of selected studies, statistical analyses, and any assessment of the risk of bias are not reported in the available material. It is therefore not possible to verify whether the review followed a systematic method or if it was primarily narrative in nature.

4. RESULTS

The main result reported in the abstract is conceptual: glucose is described as the primary stimulus for insulin secretion, while amino acids, fatty acids, and other signals can modulate it both during fasting and after a meal. Simply put, beta cells do not respond only to how much blood sugar increases, but also to the nutritional and physiological context in which this increase occurs.The review points out that nutrients and non-nutritional factors can act on shared intracellular mechanisms. Reactive oxygen species are mentioned—molecules produced during cellular metabolism that, in controlled amounts, can participate in physiological signaling but, if excessive, can contribute to cellular damage. The abstract also highlights the possibility that persistent secretory overload of beta cells promotes alterations in their function.No absolute values, total sample sizes, effect measures, statistical significance values, or aggregated quantitative results are reported in the abstract. Therefore, no verifiable numerical data are available to establish the average magnitude of the effect of each nutrient, additive, drug, or environmental factor on insulin secretion.For the book excerpt, the most relevant finding is the statement that amino acids, fatty acids, and non-nutritional factors can modulate insulin release beyond the direct action of glucose. However, the available text does not allow for assigning equal weight to all these categories of factors.

5. INTERPRETATION

From a biological perspective, insulin is a hormone that primarily helps muscles, the liver, and adipose tissue manage the nutrients available after a meal. It would therefore be unrealistic for beta cells to measure only glucose while ignoring proteins, fats, and signals originating from the gut. The synthesis proposed by the study is consistent with this integration function.The segment of the chain documented by the publication is: presence of nutrients and other physiological signals activation of mechanisms in beta cells and the gut-pancreas axis modulation of insulin secretion. Incretins, for

example, are gut hormones released after nutrient Intake that are capable of increasing insulin secretion when glucose is present. Fatty acids, on the other hand, can influence beta cells both directly and indirectly through gut signals.This interpretation does not mean that every non-carbohydrate food always increases insulin, nor that every environmental factor or additive has a clinically relevant effect. The direction and intensity of the effect can change based on the dose, the composition of the Meal, the person's metabolic state, the type of fatty acid or amino acid, and the experimental model. The publication that is the subject of the Evidence Review therefore offers a plausible biological framework, but it does not, by itself, constitute a quantitative demonstration in humans for all the claims contained in the book's paragraph.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct confirmation in humans that postprandial insulin secretion does not depend solely on glycemia comes from a physiological study on six healthy young adults. The authors compared the oral intake of 25, 50, and 100 g of glucose with intravenous infusions that reproduced similar glycemic profiles. At the same level of glycemia, oral intake produced greater insulin secretion, attributed to the incretin effect—that is, gastrointestinal signals activated by the transit of glucose through the intestine. The estimated share of the incretin effect on insulin secretion, calculated from C-peptide (an indicator of pancreatic secretion), varied from 19.2% to 61.0% depending on the oral glucose load. This directly supports the idea that, after a meal, signals other than glycemia alone contribute to the insulin response [1]. However, the sample was very small and composed of young, healthy subjects.A second study in humans evaluated how different free fatty acids modify beta-cell response. After two hours of oral fat administration and heparin infusion, followed by a hyperglycemic clamp—a procedure that maintains high and stable glycemia to study insulin secretion—the increase in non-esterified fatty acids boosted insulin, C-peptide, and proinsulin concentrations compared to the control. The increase in fatty acids was 1.7-fold for monounsaturated and saturated fats and 1.4-fold for polyunsaturated fats; the insulin response was greater after monounsaturated fats and lower after saturated fats. GLP-1, an incretin, also increased more in the test with monounsaturated fats [2]. The result confirms that the lipid component can modify the insulin response, but the experimental protocol does not coincide with a normal mixed meal and does not identify with certainty the relative contribution of individual mechanisms.Regarding amino acids, a recent experimental study used human pancreatic islets and an intestinal cell line. In batches of 15 islets, branched-chain amino acids increased insulin secretion even at low glucose concentrations. Some amino acids, including lysine, threonine, tryptophan, phenylalanine, and aspartic acid, increased GLP-1 secretion in intestinal cells. However, not all amino acid combinations further increased insulin when glucose was already elevated [3]. This confirms at the cellular level that the effect of proteins is not uniform: it depends on the amino acid composition and the glycemic context. Since this does not involve a meal consumed by people, the result does not quantify the postprandial effect in the human body.

7. CONFLICTING EVIDENCE

The book's chapter also includes food additives among the factors potentially capable of altering insulin secretion. On this point, a meta-analysis of acute clinical studies in humans offers an important note of caution. The review included 26 publications, corresponding to 34 comparisons for glycemia and 29 for insulin, and found no statistically significant differences in the postprandial insulin response between low-energy sweeteners and control interventions. The estimated mean effect on insulin was −2.39 pmol/L, with a 95% confidence interval from −11.83 to 7.05 pmol/L, which is consistent with the absence of an average acute effect [4].This evidence does not contradict the role of glucose, incretins, amino acids, and fatty acids. However, it scales back an overly broad interpretation suggesting that every food additive reliably modifies the insulin response in the short term. The certainty of the meta-analysis estimates was generally low to moderate, and the results concerned beverages or acute exposures; therefore, they do not resolve the question of long-term effects, individual compounds, or people with different metabolic conditions.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent evidence used to verify the passages relevant to the book's chapter.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Human in vitro evidence and preclinical models, according to the abstract	Glucose, nutrients, and non-nutritional factors can modulate insulin secretion	biologically consistent evidence	moderate
[1]	Comparative physiological study	6 healthy young adults	Oral glucose increased insulin secretion compared to isoglycemic intravenous infusions	direct confirmation	moderate
[2]	Experimental study in humans	Healthy adults; sample size not reported in the consulted abstract	Acute increase in free fatty acids enhanced glucose-induced insulin secretion	direct confirmation	moderate
[3]	Cellular study	Human pancreatic islets and STC-1 intestinal cells	Specific amino acids increased insulin or GLP-1 under glucose-dependent conditions	indirect confirmation	preliminary
[4]	Systematic review and meta-analysis of acute RCTs	472 participants, mostly healthy	Low-energy sweeteners did not significantly change postprandial insulin compared to controls	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication appropriately supports the book's claim that the insulin response after a meal does not depend exclusively on the increase in glycemia. Glucose remains the primary physiological stimulus, but intestinal incretins, fatty acids, and amino acids can modify the intensity and dynamics of insulin secretion.The independent evidence is particularly convincing regarding the contribution of intestinal signals and the modulation exerted by fatty acids under specific experimental conditions. The role of amino acids is supported at the cellular level but requires further validation in complete meals and diverse populations. Not all non-nutritional factors produce measurable acute effects: for low-energy sweeteners, available clinical evidence does not show an average increase in postprandial insulin.Overall, the narrative is well-supported as a physiological principle of signal integration, but it does not justify uniform generalizations regarding any additive, lifestyle habit, or environmental exposure.

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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