LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Nutrient overload, insulin resistance, and ribosomal protein S6 kinase 1, S6K1 - Review of evidence

Dott. A. Conte[1]

1 Nutritional Biologist, Italy

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 18, 2026
Updated: November 18, 2026

DOI 10.5281/zenodo.24340659

1. ABSTRACT

The analyzed publication examines the possible link between nutrient excess, activation of the mTOR/S6K1 pathway, and insulin resistance. The available material is only an abstract: it does not describe a new experiment, but synthesizes previous experimental results, including human studies with amino acid infusion. The central narrative is that high amino acid availability can increase S6K1 activity, modify IRS-1, and make insulin signaling to PI3K and AKT less efficient.In section 4.8, section 14.10, and section 15.9 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study therefore contributes to the model: nutrient → mTORC1/S6K1 → IRS-1 → reduced insulin signaling → reduced muscle glucose utilization. Independent research in humans, rodents, and cells confirms various segments of the chain. However, the effects depend on the tissue, the type of nutrient, and the IRS-1 phosphorylation site; not all regulatory sites are directly attributable to S6K1. Overall, the mechanism is well-supported at an experimental level, while its full translation into chronic human insulin resistance requires caution.

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 addressed by the publication is how an excess of nutrients, especially circulating amino acids, can contribute to reducing the insulin response. The proposed hypothesis is that mTORC1 (a protein complex that integrates nutrient and growth signals) activates S6K1, a protein that promotes protein synthesis but can also attenuate insulin signaling through IRS-1 (an adapter protein that connects the insulin receptor to the PI3K/AKT pathway).The relevance to the book's sections is precise. The publication was used to support the segment stating that an excess of amino acids increases S6K1 activity and is associated with a reduction in insulin sensitivity and muscle glucose utilization. The available text does not directly document all the steps described in the book, such as the chronic degradation of IRS-1 or the translocation of GLUT4; instead, it synthesizes a model in which persistent nutritional signaling can hinder the IRS-1 PI3K AKT pathway.Since only the abstract is available, it is not possible to verify in the provided material whether the publication presents complete original experimental data or a critical synthesis of previous studies. The abstract, in fact, uses expressions such as “recent studies” and “recent reports,” indicating that its primary role is interpretive. Therefore, the quantitative claims attributed in the book must be evaluated primarily through independent primary publications that have measured these effects.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study design, number of participants, inclusion and exclusion criteria, data collection period, infusion protocols, control groups, laboratory techniques, endpoints, statistical analyses, or follow-up are not reported in a verifiable manner.However, the abstract reports that previous results included amino acid infusions in humans and assessments of S6K1 activation, insulin-induced class 1 PI3K activity, and insulin sensitivity. It also describes a possible involvement of hVps34, a class 3 PI3K involved in intracellular nutrient sensing. The methods by which such data were obtained are not reported in the available material.Consequently, this Evidence Review does not attribute any methodological details or numerical results not present in the abstract to the analyzed publication. Verifiable experimental evidence is discussed through separate primary studies.

4. RESULTS

The main message of the abstract is that an excess of nutrients can reduce the ability of insulin to allow glucose to enter and be used by tissues. In biological terms, the cell continues to perceive an abundance of nutrients but transmits the insulin signal necessary to regulate glucose metabolism less effectively.According to the abstract, amino acids activate mTOR and S6K1. This activation is associated with the phosphorylation of IRS-1, i.e., the addition of phosphate groups to regulatory sites of the protein. The proposed result is a reduced activation of class 1 PI3K induced by insulin, and therefore insulin resistance. The abstract also states that the infusion of amino acids in humans leads to the activation of S6K1, inhibition of PI3K activation by insulin, and insulin resistance.Absolute values, sample sizes, percentages of reduction in insulin sensitivity, P-values, confidence intervals, or direct measurements of muscle glucose utilization are not reported in the available material. The data reported in the book regarding a reduction of approximately one-quarter in insulin sensitivity is therefore not verifiable in the abstract of the analyzed publication alone. However, it finds direct confirmation in the independent clinical study that compared amino acid infusion and saline solution during controlled hyperinsulinemia [1].

5. INTERPRETATION

The simplest meaning of the model is that a pathway normally useful for adapting the cell to abundance can become counterproductive if it remains highly active. After a meal, mTORC1 and S6K1 help the cell promote protein synthesis and growth. However, if the nutritional signal persists, IRS-1 can be modified in a way that less effectively links the insulin receptor to PI3K. Downstream, the activation of AKT, a protein important for many metabolic responses to insulin, may decrease.The segment actually supported by the analyzed publication is therefore: elevated amino acids activation of mTOR/S6K1 inhibition of insulin signaling mediated by IRS-1. This segment

corresponds to the sentences in the book's paragraphs that describe the transition from persistent nutrient abundance to reduced insulin sensitivity.The model does not prove that every dietary increase in protein produces clinically relevant insulin resistance, nor that S6K1 is the only mechanism involved in obesity, type 2 diabetes, or cerebral metabolic alterations. The effect observed in acute infusion experiments does not automatically equate to the effects of habitual long-term nutrition. Furthermore, the phosphorylation of IRS-1 occurs at many sites and can have different consequences depending on the tissue and the experimental context.

6. INDEPENDENT CONFIRMING EVIDENCE

The closest confirmation to the passage cited in the book comes from a human study that compared an amino acid infusion with a saline solution during a state of hyperinsulinemia similar to the postprandial state. In skeletal muscle biopsies, amino acids increased S6K1 activation to a greater extent, increased the inhibitory phosphorylation of IRS-1, and reduced insulin-induced PI3K activity. Functionally, they reduced the suppression of glucose production and insulin-stimulated glucose disposal in the muscle [1]. This is a mechanistic clinical study, highly relevant, but conducted under acute experimental conditions and not designed to demonstrate the effects of chronic dietary exposure.A previous crossover study conducted on seven healthy men showed that an acute increase in plasma amino acids reduced glucose disposal and muscle glycogen synthesis. The design with saline control and controlled hormone maintenance allows the result to be attributed to amino acids with greater certainty than simple dietary observations [2]. This work confirms the direction of the metabolic effect reported in the book, but it did not directly define the entire mTORC1/S6K1/IRS-1 chain.Independent molecular confirmation was obtained in liver and muscle cells. In this model, glucose and leucine activated mTOR in a Raptor-dependent manner, a structural component of mTORC1, promoting the phosphorylation of IRS-1 at the Ser636/639 sites. Modifications that mimicked this phosphorylation reduced the insulin-induced PI3K activation associated with IRS-1; the reduction of Raptor or the activation of the AMPK pathway attenuated this blockade [3]. The result confirms the link between nutrients, mTOR, and reduced PI3K/AKT signaling, but it derives primarily from cellular systems and does not, on its own, demonstrate human physiology.In rats made obese with a high-fat diet, the basal activity of mTOR and S6K1 was higher in the liver and muscle compared to lean controls. This hyperactivation was associated with greater phosphorylation of IRS-1 at Ser636/639 and lower AKT activation. In liver cells, the inhibition of mTOR/S6K1 with rapamycin reduced IRS-1 phosphorylation and rapidly increased the PI3K activity associated with IRS-1 and the phosphorylation of AKT [4]. This is biologically consistent evidence with experimental causal support, but diet-induced obesity in rats does not fully reproduce human type 2 diabetes.Taken together, these studies build a convergent chain: amino acids can acutely reduce muscle glucose utilization in humans; in a controlled human protocol, this effect is accompanied by greater S6K1 activity and lower PI3K signaling; in cells and animals, persistent activation of mTOR/S6K1 can modify IRS-1 and attenuate the signal toward AKT [1,2,3,4].

7. CONFLICTING EVIDENCE

An important clarification concerns the idea that S6K1 always phosphorylates IRS-1 at the same sites and with the same consequences. In primary human adipocytes, a study evaluated the Ser307 site of IRS-1. Genetic or pharmacological inhibition of S6K1 reduced the phosphorylation of the S6 protein, confirming the efficacy of S6K1 inhibition, but did not reduce the phosphorylation of IRS-1 at Ser307. The authors therefore concluded that, in these cells and for this site, S6K1 was not the physiological kinase responsible for the phosphorylation [5].This evidence does not directly contradict the results on S6K1 activation by amino acids or on muscle insulin resistance. However, it indicates that it is incorrect to indiscriminately attribute every phosphorylation of IRS-1 to S6K1. The mechanism depends on the regulatory site studied, the cell type, and the stimulus. In the book's model, the most solid message remains the negative feedback of the mTORC1/S6K1 axis on insulin signaling; the detail of the individual IRS-1 residue, however, requires a more cautious formulation.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to verify the individual steps of the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Scientific summary; abstract only available	Not reported in available material	Proposes that elevated amino acids activate S6K1 and impair IRS-1-mediated insulin signaling	biologically consistent evidence	preliminary
[1]	Mechanistic clinical study	Adults undergoing amino acid or saline infusion during hyperinsulinemia	Amino acids increased S6K1 and inhibitory phosphorylation of IRS-1, reducing PI3K and glucose disposal	direct confirmation	moderate
[2]	Human crossover study	Seven healthy men	Acute increase in amino acids reduced glucose disposal and muscle glycogen synthesis	direct confirmation	moderate
[3]	Cellular and molecular	Hepatic, muscle, and human embryonic cells	Nutrients and mTOR/Raptor increased IRS-1 phosphorylation and reduced PI3K/AKT signaling	indirect confirmation	moderate
[4]	Animal and cellular	Obese rats fed a high-fat diet and HepG2 cells	Increased mTOR/S6K1 was associated with greater IRS-1 phosphorylation and lower AKT activation	biologically consistent evidence	moderate
[5]	Cellular	Human primary adipocytes	S6K1 was not found to be responsible for IRS-1 phosphorylation at the Ser307 site	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication contributes significantly to the narrative that an excess of amino acids can temporarily reduce insulin sensitivity through the activation of the mTORC1/S6K1 axis and negative feedback on IRS-1. The core of this chain is confirmed by experimental human data and by cellular and animal models.The evidence is particularly robust regarding the acute effect of elevated amino acids on glucose metabolism in muscle and the involvement of mTOR/S6K1 in the negative regulation of insulin signaling. However, it remains to be defined to what extent this mechanism, on its own, contributes to chronic insulin resistance across different populations and tissues. Furthermore, it is not appropriate to attribute every phosphorylation of IRS-1 to S6K1 without specifying the site and the model studied.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Mechanism of Amino Acid-Induced Skeletal Muscle Insulin Resistance in Humans**
Krebs et al., 2002
Diabetes
DOI: https://doi.org/10.2337/diabetes.51.3.599

[2] **Nutrients Suppress Phosphatidylinositol 3-Kinase/Akt Signaling via Raptor-Dependent mTOR-Mediated Insulin Receptor Substrate 1 Phosphorylation**
Tzatsos et al., 2006
Molecular and Cellular Biology
DOI: https://doi.org/10.1128/MCB.26.1.63-76.2006

[3] **Phosphorylation of IRS1 at Serine 307 in Response to Insulin in Human Adipocytes Is Not Likely to be Catalyzed by p70 Ribosomal S6 Kinase**
Rajan et al., 2013
PLoS ONE
DOI: https://doi.org/10.1371/journal.pone.0059725

[4] **Overactivation of S6 Kinase 1 as a Cause of Human Insulin Resistance During Increased Amino Acid Availability**
Tremblay et al., 2005
Diabetes
DOI: https://doi.org/10.2337/diabetes.54.9.2674

[5] **Increased Activation of the Mammalian Target of Rapamycin Pathway in Liver and Skeletal Muscle of Obese Rats: Possible Involvement in Obesity-Linked Insulin Resistance**
Khamzina et al., 2005
Endocrinology
DOI: https://doi.org/10.1210/en.2004-0921