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# BIOACTIVE PEPTIDES AND REGULATION OF ENERGY METABOLISM: EVIDENCE ON WEIGHT CONTROL AND INSULIN SENSITIVITY - SYSTEMATIC REVIEW

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## ABSTRACT

Obesity, insulin resistance, and changes in energy metabolism pose important public health challenges due to their association with type 2 diabetes mellitus, metabolic syndrome, low-grade chronic inflammation, and increased cardiometabolic risk. In this context, bioactive peptides have attracted growing scientific interest because of their ability to modulate pathways related to satiety, glycemic homeostasis, insulin signaling, metabolic inflammation, energy expenditure, and substrate oxidation. The aim of this systematic review was to analyze the available evidence regarding bioactive peptides and their relationship with body weight control and insulin sensitivity. A total of 45 studies were included, encompassing reviews, in vitro studies, preclinical models, observational studies, and randomized clinical trials. The studies were organized into six thematic axes: dietary bioactive peptides, intestinal peptides that regulate satiety, amylin analogs, GLP-1 agonists, dual agonists and incretin triagonists, and mitochondrial/ metabolic peptides.The results indicated that food-derived peptides from soy, egg, milk, quinoa, fish, and macroalgae show glucoregulatory potential, especially through DPP-IV inhibition, modulation of digestive enzymes, improved insulin signaling, and reduced metabolic inflammation. However, this evidence is still predominantly experimental. In contrast, GLP-1 agonists, tirzepatide, retatrutide, pramlintide, PYY3-36, and oxyntomodulin showed greater clinical robustness, with effects on weight reduction, satiety, glycemic control, and energy expenditure. Peptides such as MOTS-c and adropin broadened understanding of mechanisms related to metabolic flexibility and mitochondrial function. It is concluded that bioactive peptides represent a promising platform for regulating energy metabolism, with applications ranging from functional nutrition to advanced metabolic pharmacology.

**Keywords:**bioactive peptides; energy metabolism; obesity; insulin resistance.

# INTRODUCTION

Obesity, insulin resistance, and changes in energy metabolism are among the main contemporary challenges in public health, due to their direct association with type 2 diabetes mellitus, metabolic syndrome, metabolic fatty liver disease, dyslipidemias, low-grade chronic inflammation, and increased cardiovascular risk. In this context, controlling body weight and improving insulin sensitivity do not depend solely on calorie restriction, but on a complex interaction among food intake, energy expenditure, hormonal signaling, the intestinal microbiota, adipose tissue, skeletal muscle, the liver, the gut-brain axis, and mitochondrial function. Understanding these mechanisms has driven research into bioactive molecules capable of modulating specific metabolic pathways, among which bioactive peptides have received increasing attention.

Bioactive peptides are short sequences of amino acids, generally released from the hydrolysis of dietary proteins, digestive processes, fermentation, endogenous metabolism, or pharmacological development, capable of exerting specific physiological effects on organ systems. Different studies have shown that these compounds may have antidiabetic, anti-obesity, antioxidant, anti-inflammatory, anti-hypertensive, and modulatory properties on lipid and glycemic metabolism (1–3). In the metabolic context, bioactive peptides can act through multiple mechanisms, including inhibition of dipeptidyl peptidase IV (DPP-IV), modulation of the enzymes α-amylase and α-glucosidase, stimulation of incretin secretion, improvement of insulin signaling, activation of pathways such as Akt and AMPK, reduction of inflammation in adipose tissue, and effects on satiety and energy intake (1,2,4, 17,20).

Among the dietary sources investigated, peptides derived from soy, egg, milk, quinoa, fish, macroalgae, and protein hydrolysates stand out. Peptides obtained from germinated soy have demonstrated antidiabetic potential through the inhibition of DPP-IV, α-amylase, and α-glucosidase, suggesting an effect on postprandial glycemic control and on the incretin axis (4). Similarly, hydrolysates and peptides derived from egg white have been associated with improved insulin resistance in cellular and animal models, with effects on inflammatory pathways,

insulin signaling, and activation of the Akt protein (5–7). Preclinical studies also indicate that peptides derived from bovine α-lactalbumin may reduce adipose tissue inflammation and insulin resistance in models fed a high-lipid diet (8). These findings reinforce

Scientific interest in food peptides as functional components capable of modulating metabolic disorders associated with excess weight.

In addition to food peptides, there is growing interest in endogenous peptides and peptide hormones involved in the regulation of satiety, energy balance, and glycemic homeostasis. The YY3-36 peptide, for example, has demonstrated the ability to reduce food intake in physiological models and in individuals with obesity, reinforcing the importance of the gut-brain axis in appetite control (21,22). Alterations in PYY release in obese individuals have also been associated with reduced satiety, suggesting that intestinal hormonal dysfunctions may contribute to the maintenance of excess weight (23). Oxintomodulin, another intestinal peptide, has shown effects on reducing body weight, decreasing energy intake, increasing energy expenditure, and improving glycemic regulation, indicating therapeutic potential in the treatment of obesity and glycemic alterations (24– 26). Combined strategies involving GLP-1, oxintomodulin, and PYY have also shown favorable effects on body weight and glycemia in individuals with obesity, prediabetes, or type 2 diabetes (27).

The amilinin pathway also represents a relevant axis in the regulation of appetite and body weight. Pramlintide, a synthetic analog of amylin, has been evaluated in clinical trials with obese individuals, showing progressive weight reduction and potential for weight maintenance when combined with lifestyle interventions (28,29). In addition, neurohormonal combinations, such as pramlintide in combination with metreleptin, have demonstrated greater weight loss, suggesting that a therapeutic approach based on multiple peptide signals may offer superior metabolic benefits compared with isolated strategies (30). These findings anticipate a trend observed in modern metabolic therapies: the development of peptide drugs that act simultaneously on different hormone pathways related to satiety, insulin secretion, ene-

rgy expenditure, and substrate metabolism.

Among the most clinically robust peptide therapies, glucagon-like peptide 1 receptor agonists (GLP-1) stand out. Liraglutide 3.0 mg demonstrated efficacy in reducing body weight in adults with overweight or obesity, including individuals with type 2 diabetes and patients using basal insulin, linking weight loss to improvements in glycemic parameters (31–33). Subsequently, semaglutide 2.4 mg consolidated even more expressive clinical evidence, with trials from the STEP series showing clinically significant weight loss, improved glycemic outcomes, benefit in combination with intensive behavioral therapy, weight maintenance with continued treatment, and effects sustained for up to two years (34–38). These results position GLP-1 agonists as one of the most relevant classes at the intersection of obesity treatment, glycemic control, and improved metabolic risk.

The pharmacological evolution of metabolic peptides has also led to the development of dual agonists and triple agonists, capable of simultaneously activating receptors involved in energy regulation. Tirzepatide, a dual agonist of the GIP and GLP-1 receptors, has demonstrated significant reductions in body weight in adults with obesity or overweight, as well as improved glycemic parameters in individuals with type 2 diabetes (39,40). More recently, retatrutide, an agonist of the GLP-1, GIP, and glucagon receptors, showed promising results in a phase 2 study, reinforcing the hypothesis that multi-hormonal agonism may broaden the effects on weight loss, energy metabolism, and glycemic control (41). These findings indicate that the field of peptide therapies has advanced from isolated interventions to integrated models of metabolic regulation.

Another emerging axis involves mitochondrial peptides and systemic regulators of energy homeostasis, such as MOTS-c and adropin. MOTS-c, a peptide derived from the mitochondrion, has shown the ability to promote metabolic homeostasis, reduce obesity, and improve insulin resistance in experimental models (42). In humans, circulating levels of MOTS-c have been associated with insulin sensitivity in lean individuals, although this relationship appears to be altered in obese individuals, suggesting possible

interference from the metabolic state in the signaling of this peptide (43). Adropin, in turn, has been identified as a secreted factor related to macronutrient intake, energy homeostasis, lipid metabolism, and the preference for substrate oxidation in skeletal muscle (44,45). These peptides expand the understanding of energy metabolism beyond the gastrointestinal axis, incorporating mechanisms related to mitochondrial function, metabolic flexibility, and the selection of energetic substrates.

Despite the significant growth of the evidence, the field of bioactive and metabolic peptides still shows important methodological heterogeneity. While incretin agonists and multi-agonists have multicenter randomized clinical trials with consistent results, many food peptides are still investigated predominantly in in vitro and preclinical models. This difference in the level of evidence makes direct comparison between interventions, peptide sources, mechanisms of action, and clinical relevance difficult. In addition, aspects such as bioavailability, gastrointestinal stability, effective dose, long-term safety, interaction with diet, impact on the intestinal microbiota, and applicability in populations with obesity, insulin resistance, or type 2 diabetes still require further in-depth investigation.

In this scenario, it becomes relevant to systematize the available evidence on bioactive peptides and the regulation of energy metabolism, considering their effects on weight control, insulin sensitivity, satiety, energy expenditure, and glycemic homeostasis. Thus, this systematic review aims to critically analyze studies on dietary bioactive peptides, gastrointestinal peptides, hormonal analogs, incretin agonists, multiagonists, and mitochondrial peptides, seeking to understand their contribution to weight control and improved insulin sensitivity across different levels of evidence.

## METHODOLOGY

This is a systematic literature review, developed with the objective of analyzing the available scientific evidence on the relationship between bioactive peptides and the regulation of energy metabolism, with an emphasis on the effects on body

weight control, insulin sensitivity, satiety, energy expenditure, and glycemic homeostasis. The methodological conduct was structured according to the general principles recommended for systematic reviews, prioritizing transparency in the search strategy, a priori definition of eligibility criteria, careful selection of studies, and qualitative synthesis of the findings.

The guiding question was formulated based on the following question: what evidence is available regarding the action of bioactive peptides—dietary, gastrointestinal, hormonal, incretin-based, multiagonist, and mitochondrial—in the regulation of energy metabolism, control of body weight, and insulin sensitivity? To guide the selection of studies, the population or model of interest was considered to include individuals with overweight, obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, or related experimental models; as the intervention or exposure, dietary bioactive peptides, protein hydrolysates, gastrointestinal peptides, amylin analogs, GLP-1 agonists, dual or triagonist incretin agonists, MOTS-c, and adropin; and as the main outcomes, changes in body weight, food intake, satiety, energy expenditure, insulin sensitivity, glucose tolerance, glycemic control, metabolic inflammation, insulin signaling, and substrate metabolism.

The bibliographic search was conducted in recognized scientific databases, including PubMed/MEDLINE, PubMed Central, ScienceDirect, SpringerLink, Wiley Online Library, Cambridge Core, Nature, The New England Journal of Medicine, The Lancet, JAMA Network, Diabetes Care, Cell Metabolism, Nutrients, Food Chemistry, Journal of Functional Foods, European Journal of Nutrition and International Journal of Molecular Sciences. Official editorial pages and records with DOI were also considered when available, in order to ensure traceability of the included studies. The search strategy combined controlled descriptors and free-text terms in English related to the topic, such as “bioactive peptides”, “food-derived peptides”, “energy metabolism”, “obesity”, “body weight”, “weight loss”, “insulin sensitivity”, “insulin resistance”, “type 2 diabetes”, “DPP-IV inhibitory peptides”, “GLP-1 receptor agonist”, “tirzepatide”, “semaglutide”, “liraglutide”, “oxyntomodulin”, “peptide YY”, “pramlintide”, “MOTS-c” and “adropin”. These

terms were combined using Boolean operators, especially “AND” and “OR”, to broaden the sensitivity of the search and, at the same time, maintain direct alignment with the research question.

Studies published in peer-reviewed scientific journals were included, available in full text or with complete bibliographic information, addressing directly the relationship between bioactive peptides and metabolic outcomes associated with weight control, insulin sensitivity, energy metabolism, or glycemic homeostasis. Relevant reviews were eligible to support the conceptual basis, as were in vitro studies, pre-clinical studies in animal models, observational studies in humans, experimental clinical trials, and randomized clinical trials. Given the translational nature of the topic, different levels of evidence were included, provided there was coherence with the review’s objectives and adequate bibliographic traceability.

Studies with no direct relationship to energy metabolism, weight control, insulin sensitivity, or glycemic regulation were excluded; articles without sufficient bibliographic identification; publications lacking DOI, PMID, reliable editorial page information, or minimum traceability data; duplicate studies; conference abstracts without a corresponding full article; opinion publications without an empirical basis or structured review; and studies that addressed peptides only in isolated biochemical terms, without connection to the metabolic outcomes investigated. References whose identification could not be satisfactorily confirmed during the bibliographic validation stage were also excluded.

The selection process occurred in successive stages. Initially, titles and abstracts were assessed for thematic relevance. Next, potentially eligible studies were examined in greater detail, considering the type of peptide evaluated, the population or experimental model, study design, metabolic outcomes, and contribution to the review question. After this screening, the references were submitted for bibliographic validation, noting full title, authorship, year of publication, journal, volume, issue, pages or electronic identifier, and DOI. At the end, 45 studies were selected to form the review base, distributed across evidence on dietary bioactive peptides,

regulatory gastrointestinal satiety peptides, amylin analogs, GLP-1 agonists, dual agonists and incretin triagonists, as well as mitochondrial peptides and regulators of energy homeostasis.

Data extraction was carried out in a standardized manner, considering the following information: author and year of publication, country or study context, type of study, peptide or peptide class evaluated, study population or experimental model, main metabolic findings, and contribution to the systematic review. To make the presentation of results more appropriate to the format of scientific publication, the studies were subsequently grouped by thematic axis, avoiding the presentation of an excessively extensive table in the body of the article. Thus, the main synthesis was organized into six categories: food-derived bioactive peptides with glucoregulatory action; intestinal regulatory peptides of satiety and energy intake; amylin analogs and neurohormonal strategies; GLP-1 receptor agonists; dual agonists and incretin triagonists; and mitochondrial peptides or regulators of energy homeostasis.

The data analysis was conducted through qualitative and narrative synthesis, considering the heterogeneity of the methodological designs, populations, experimental models, interventions, and outcomes assessed. No quantitative meta-analysis was performed, since the included studies showed wide diversity regarding the type of peptide, dose, route of administration, intervention duration, biological model, measured metabolic parameters, and level of evidence. The synthesis of findings aimed to identify convergences, limitations, recurring biological mechanisms, and gaps in knowledge, especially regarding the translation of pre-clinical evidence into clinical practice.

For interpretation purposes, the studies were classified into three main levels of evidence. The first level included randomized clinical trials and clinical studies with direct peptide intervention in humans, especially those involving liraglutide, semaglutide, tirzepatide, retatrutide, pramlintide, oxintomodulin, and PYY. The second level included pre-clinical studies and mechanistic, particularly those with food-derived peptides, protein hydrolysates, MOTS-c, and adropin. The third level included reviews

and studies of conceptual support used to contextualize mechanisms of action, such as inhibition of DPP-IV, modulation of digestive enzymes, insulin signaling, anti-inflammatory activity, and regulation of satiety.

Because this is a systematic review based on secondary data previously published, with no collection of individual information, no intervention in human beings, and no use of identifiable data, there was no need to submit to an Ethics Committee for Research. All included studies were properly referenced, preserving the integrity of the original sources and the scientific traceability of the information used.

## RESULTS

This systematic review included 45 studies that investigated the relationship between bioactive peptides and the regulation of energy metabolism, focusing on body weight control, insulin sensitivity, satiety, energy expenditure, and glycemic homeostasis. The selected studies covered different levels of evidence, including conceptual-support reviews, in vitro studies, preclinical models, observational studies in humans, experimental clinical trials, and multicenter randomized clinical trials.

The analysis of the studies showed substantial heterogeneity regarding the origin of the peptides, the methodological design, the populations evaluated, and the metabolic outcomes investigated. To better organize the findings, the studies were grouped into six thematic axes: dietary bioactive peptides with glucoregulatory action; intestinal peptides that regulate satiety and energy intake; amylin analogs and neuro-hormonal strategies; GLP-1 receptor agonists; dual agonists and incretin triagonists; and mitochondrial peptides or regulators of energy homeostasis.

It was observed that the dietary bioactive peptides corresponded to the largest group of included studies, with a predominance of experimental and preclinical evidence. These studies addressed peptides derived from soy, egg, milk, quinoa, fish, macroalgae, and other protein hydrolysates, with an emphasis on mechanisms such as DPP-IV inhibition, modulation of digestive enzymes, improved insulin signaling, and reduced met-

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abolic inflammation (1–20). On the other hand, studies involving GLP-1 agonists, tirzepatide, retatrutide, pramlintide, oxintomodulin, and PYY presented a higher density of clinical evidence, especially regarding weight reduction, glycemic control, and modulation of satiety (21–41). The mitochondrial and metabolic peptides, mainly represented by MOTSc and adropin, contributed to expanding understanding of metabolic flexibility, substrate oxidation, and systemic regulation of energy homeostasis (42–45)

**Table 1 - Distribution of the Included Studies by Thematic Axis and Type predominant evidence**

| T hematic axis | Studies in l i d s | Number o f t o | Type p d mi a t d idên i | P ptíd l s v liad | P in ip l ont ib ição |
|---|---|---|---|---|---|
| Food bioactive peptides with glucoregulatory action | 1–20 | 20 | Revisions, studies in vitro and studies pre-clinical | Peptides derived from soy, egg, milk, quinoa, fish, macroalgae, and protein hydrolysates | They show potential for glycemic modulation through DPP-IV inhibition, improved insulin signaling, and reduced metabolic inflammation. |
| Regulatory intestinal peptides of satiety and energy intake | 21–27 | 7 | Studies mechanistic and clinical experimental | PYY3-36, oxyntomodulin, and GLP-1/oxyntomodulin/PYY combination | They demonstrate effects on appetite, satiety, energy intake, energy expenditure, and glycemia. |
| Amylin analogs and neurohormonal strategies | 28–30 | 3 | Clinical trials and pharmacological studies | Pramlintide and pramlintide/metreleptin | Strengthen the amylin pathway as a relevant peptide target for reducing and maintaining body weight. |
| GLP-1 receptor agonists | 31–38 | 8 | Clinical trials randomized multicenter | Liraglutide and semaglutide | They provide robust clinical evidence for weight loss, glycemic improvement, and weight maintenance. |

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|---|---|---|---|---|---|
| Dual and tri-agonists of incretin | 39–41 | 3 | Randomized clinical trials and phase 2 study | Tirzepatide and retatrutide | They show a greater metabolic impact through simultaneous activation of the GIP, GLP-1, and glucagon pathways. |
| Mitochondrial peptides and regulators of energy homeostasis | 42–45 | 4 | Preclinical, mechanistic, and observational studies | MOTS-c and adropin | They expand understanding of peptides as regulators of substrate oxidation, insulin sensitivity, and metabolic flexibility. |

The distribution of studies showed that bioactive dietary peptides represent an area of major scientific growth, although it is still characterized by a predominance of experimental studies. Within this group, the studies highlighted effects metabolic

promising, especially in models of insulin resistance, syndrome metabolic and type 2 diabetes. Egg-derived peptides showed a relevant role in modulating insulin signaling, with effects on inflammatory pathways, Akt, and AMPK (5–13). Plant-derived peptides, such as soybean and quinoa, showed potential to inhibit enzymes related to glycemic metabolism, such as DPP-IV, α-amylase, and α-glucosidase (3,4,16). Meanwhile, peptides derived from milk, fish, and macroalgae helped reinforce the incretin and digestive action axis, mainly through inhibition of DPP-IV and modulation of the secretion of GLP-1, GIP, and insulin (14–20).

In studies involving intestinal peptides, the findings indicated that PYY3-36 and oxyntomodulin exert relevant effects on food intake, energy expenditure, and glycemic homeostasis. PYY3-36 was associated with reduced food intake and increased satiety, while oxyntomodulin demonstrated a dual effect, decreasing energy intake and increasing energy expenditure in overweight or obese individuals (21–26). The combination of GLP-1, oxyntomodulin, and PYY showed simultaneous benefits on body weight and glycemia, suggesting that multihormonal strategies may, in part, mimic

metabolic responses associated with integrated intestinal signaling (27).

The analogs of amylin, especially a pramlintide, demonstrated potential for progressive reduction in body weight and maintenance of weight loss when combined with lifestyle interventions. A the combination pramlintide/metreleptin also showed a greater effect on weight loss, indicating that combined neurohormonal approaches may enhance therapeutic responses in individuals with obesity (28–30). These findings reinforce that weight control involves multiple peptidergic pathways related to satiety, central signaling, and neuroendocrine regulation.

Among the clinical studies with the greatest robustness, GLP-1 receptor agonists stood out. Liraglutide 3.0 mg showed efficacy in reducing weight in adults who were overweight or obese, including populations with type 2 diabetes and individuals using basal insulin (31–33). Semaglutide 2.4 mg demonstrated even more striking results, with clinically significant reductions in body weight, improved glycemic control, benefit in combination with intensive behavioral therapy, and maintenance of effects in the long term when treatment was continued (34–38). These studies formed the most consistent body of clinical evidence from the review.

Dual and triagonist incretin agonists represented an important evolution in peptide therapies. Tirzepatide, by activating the GIP and GLP-1 receptors, demonstrated substantial reductions in body weight in adults with obesity or overweight, alongside improved glycemic outcomes in individuals with type 2 diabetes (39,40). Retatrutide, an agonist of the GLP-1, GIP, and glucagon receptors, showed promising results in a phase 2 study, suggesting that simultaneous stimulation of multiple hormonal axes may enhance the effects on weight loss and energy metabolism (41).

Finally, mitochondrial peptides and regulators of energy homeostasis added a relevant mechanistic dimension. MOTS-c was associated with improved metabolic homeostasis, reduced insulin resistance, and protection against obesity in experimental models, while human studies observed an association between circulating levels of MOTS-c and insulin sensitivity in lean individuals (42,43). Adrop-

in, in turn, has been linked to the regulation of macronutrient intake, lipid metabolism, and substrate oxidation preference in skeletal muscle (44,45). These findings indicate that certain Peptides act not only on satiety or hormonal secretion, but also in cellular processes related to metabolic flexibility and the use of energy substrates.

**Table 2 - Synthesis of the main metabolic mechanisms identified in the included studies**

| M ni mo m t bóli o id ntifi do | P ptíd o ou la la ionado | E tudo la ion d | D f ho m tabóli os a iado | Int p tação dos a hado |
|---|---|---|---|---|
| Inhibition of DPP-IV and modulation ofthe incretin axis | Soy, milk, fish, macroalgae, quinoa peptides, and protein hydrolysates | 4,14–20 | Potential increase in incretin activity, improved insulin secretion, and glycemic regulation | Represents one of the most frequent mechanisms among dietary peptides, although still with a predominance of in vitro and preclinical evidence. |
| Modulation of digestive enzymes involved in carbohydrate metabolism | Soy and quinoa peptides | 4,16 | Inhibition of α-amylase and α-glycosidase, with possible reduction of the postprandial glycemic response | Suggests a potential application of dietary peptides in glycemic control associated with the digestion and absorption of carbohydrates. |
| Improves insulin signaling in metabolic tissues | Peptides derived from egg white, IRW, and protein hydrolysates | 5–13 | Increased signaling via Akt and AMPK improves glucose tolerance and insulin sensitivity | Demonstrates a direct metabolic effect in skeletal muscle, liver, and adipose tissue, especially in insulin resistance models. |
| Reduction of metabolic inflammation | Egg, milk, and protein hydrolysate peptides | 6,8, 10–13 | Mitigation of inflammatory changes associated with obesity, adipose tissue, and metabolic syndrome | Strengthens the link between the peptides' anti-inflammatory action and improved insulin sensitivity. |
| Increased satiety and reduced food intake | PYY3-36, oxyntomodulin, pramlintide, GLP- 1, and combined therapies | 21–31,34–41 | Reduced energy intake, weight loss, and improved appetite control | Highlights the role of the gut–brain axis and neuroendocrine signaling in weight regulation. |
| Increase in energy expenditure and modulation of energy balance | Oxinomodulin, retatrutide, adropin, and MOTS-c | 24–27,41–45 | Elevation of energy expenditure, regulation of substrate oxidation, and improvement of energy homeostasis | It indicates that some peptides act not only by reducing food intake, but also by modifying energy metabolism. |

| | | | | |
|---|---|---|---|---|
| Clinical improvement in body weight and blood glucose | Liraglutide, semaglutide, tirzepatide, and retatrutide | 31–41 | Significant weight loss, reduction in glycemic parameters, and long-term weight maintenance | It constitutes the most robust set of clinical evidence from the review, with a direct impact on obesity and type 2 diabetes. |
| Regulation of metabolic flexibility and substrate oxidation | MOTS-c and adropin | 42–45 | Improves insulin resistance, lipid metabolism, and the preference for substrate oxidation in muscle | Expands understanding of peptides as systemic mediators of energy homeostasis and mitochondrial function. |

Overall, the results indicated that bioactive peptides act on multiple levels of metabolic regulation. Dietary peptides showed potential mainly through enzymatic, anti-inflammatory mechanisms and improvement of insulin signaling, although most of the evidence is still focused on preclinical or in vitro studies. Gastrointestinal peptides, hormonal analogs, and peptide drugs, on the other hand, presented more robust clinical evidence, especially in outcomes related to weight reduction, glycemic control, and modulation of satiety.

The synthesis of the findings suggests that the effects of bioactive peptides on energy metabolism and insulin sensitivity do not occur through a single mechanism. Instead, they involve a network of integr - ated actions that includes digestion and absorption of carbohydrates, the incretin axis, insulin secretion, muscle and hepatic signaling, inflammation in adipose tissue, satiety, energy expenditure, mitochondrial function, and metabolic flexibility. This diversity of mechanisms explains the growing relevance of peptides both as functional components of dietary origin and as a foundation for modern pharmacological therapies aimed at treating obesity and type 2 diabetes.

## DISCUSSION

The findings of this systematic review demonstrate that bioactive peptides constitute a broad and heterogeneous class of molecules with relevant potential in regulating energy metabolism, controlling body weight, and improving insulin sensitivity. Analysis of the 45 included studies showed that peptides may act

through different physiological and molecular pathways, including modulation of the incretin axis, inhibition of digestive enzymes, improvement of insulin signaling, reduction of metabolic inflammation, regulation of satiety, increased energy expenditure, control of substrate oxidation, and influence on mitochondrial function. This diversity of mechanisms reinforces the importance of peptides as multifunctional metabolic agents, both in the field of functional nutrition and in the development of therapies modern pharmacological.

One of the main findings of this review was the distinction between the levels of evidence available for different peptide classes. Food-derived bioactive peptides showed a predominance of in vitro, preclinical studies, and mechanistic reviews, whereas GLP-1 agonists, dual GIP/GLP-1 agonists, and incretin triagonists concentrated more robust clinical evidence, especially through multicenter randomized clinical trials (31–41) . This difference is relevant because it indicates that, although food peptides have important biological plausibility, there is still a translational gap between experimental findings and their direct clinical application in humans. In contrast, peptide-based drugs that act on specific hormonal pathways have already demonstrated consistent clinical impact in obesity and type 2 diabetes.

Soy-, egg-, milk-, quinoa-, fish-, and macroalgae-derived food peptides demonstrated promising mechanisms related to glycemic control and insulin resistance. Among the most recurring mechanisms, inhibition of dipeptidyl peptidase IV (DPP-IV) stood out—an enzyme responsible for degrading incretins such as GLP-1 and GIP. Inhibiting this enzyme may help prolong incretin activity, promoting glucose-dependent insulin secretion and improving glycemic control (4, 14–20). In addition, some peptides showed the ability to inhibit α-amylase and α-glucosidase, suggesting a possible effect on the digestion and absorption of carbohydrates, with a potential impact on postprandial glycemia (4, 16). These findings bring food peptides closer to metabolic strategies already established in the treatment of diabetes, although it is still necessary to prove their clinical efficacy in controlled human studies.

Another relevant aspect was the role of food-derived peptides in insulin signaling in metabolically active tissues. Studies with peptides derived from egg white, including protein hydrolysates and specific sequences such as IRW, showed improved glucose tolerance, activation of pathways such as Akt and AMPK, and attenuation of diet-induced insulin resistance from a high-fat diet or inflammatory stimuli (5–13). Akt pathway activation is particularly relevant due to its relationship with insulin-mediated glucose uptake, while AMPK acts as a cellular energy sensor, promoting fatty acid oxidation, glucose uptake, and energy balance. Thus, the results suggest that certain food-derived peptides may act not only in nutrient digestion or on the incretin axis, but also in pathways intracellular directly related to insulin sensitivity.

The relationship between metabolic inflammation and insulin resistance also appeared as an important axis in the evaluated studies. Obesity is often accompanied by chronic low-grade inflammation in adipose tissue, with the involvement of pro-inflammatory cytokines, oxidative stress, and adipocyte dysfunction. Studies included in this review showed that egg white hydrolysates and bovine α-lactalbumin were able to modulate inflammatory markers and improve insulin resistance in experimental models (6,8, 10–13). This observation is relevant because it reinforces the hypothesis that some of the metabolic effects of bioactive peptides may result from reducing systemic and tissue inflammation, favoring an improved response to insulin.

Despite these promising findings, clinical extrapolation of food-derived peptides should still be done with caution. Much of the research uses models cellular, digestion simulated gastrointestinal conditions or animals fed hyperlipidemic diets. Although these models are useful for identifying mechanisms and selecting bioactive candidates, they do not reproduce fully the the complexity of human metabolism. Aspects such as bioavailability, gastrointestinal stability, intestinal absorption, hepatic metabolism, effective dose, food matrix, interaction with the microbiota, and long-term safety still represent important limitations. Therefore, at this time, food-derived peptides should be interpreted as compounds with functional and

translational potential, but still dependent on further clinical validation.

In contrast, gastrointestinal peptides and peptide-based drugs showed more consistent clinical evidence. PYY3-36 demonstrated reducing food intake and increasing satiety, reinforcing the role of the gut–brain axis in appetite regulation (21,22) . The lower release of PYY observed in obese individuals suggests that intestinal hormonal alterations may contribute to impairments in perceived satiety and to the maintenance of a positive energy balance (23) . These findings indicate that obesity should not be understood only as a result of excessive caloric intake, but as a condition associated with complex neuroendocrine changes that influence hunger, satiety, food reward, and energy expenditure.

Oxyntomodulin also stood out for having a dual action in reducing energy intake and increasing energy expenditure (24,25) . This profile is particularly relevant, since most anti-obesity interventions act predominantly by reducing food intake. The possibility of simultaneously modulating appetite and energy expenditure makes oxyntomodulin and related strategies attractive for the development of metabolic therapies. In addition, the glucoregulatory effects of the oxyntomodulin, including independent of weight loss, suggest that their benefits may involve direct mechanisms on hormonal secretion, insulin sensitivity, and glycemic homeostasis (26). The combination of GLP-1, oxyntomodulin, and PYY reinforces the rationale for multihormonal therapies, which are capable of partially reproducing the integrated intestinal signaling observed after dietary changes or metabolic interventions (27).

The amylin pathway, represented by pramlintide, showed an important contribution to weight control. Pramlintide demonstrated a progressive reduction in body weight and favored maintenance of weight loss when combined with a behavioral intervention (28,29). The pramlintide/metreleptin combination also suggested potential to amplify weight-loss effects through an integrated neurohormonal approach (30). These findings indicate that modulation of satiety and central control of food intake does not

depend exclusively on the GLP-1 axis, but may involve other anorexigenic peptides with complementary action.

GLP-1 receptor agonists were the group with the greatest clinical consistency in this review. Liraglutide 3.0 mg showed efficacy in weight reduction in individuals with overweight or obesity, including patients with type 2 diabetes and patients using basal insulin (31–33). However, the most striking results were observed in studies with semaglutide 2.4 mg, which demonstrated clinically significant reductions in body weight, improvement in glycemic parameters, additional benefit when combined with intensive behavioral therapy, and maintenance of effects with continued treatment (34–38). These results reinforce the central role of GLP-1 agonism in contemporary obesity therapy,
especially by integrating effects on satiety, gastric emptying, glucose-dependent insulin secretion, and glycemic control.

The emergence of dual and triagonists represents one of the most important developments in the field. Tirzepatide, a dual GIP/GLP-1 agonist, showed significant reductions in body weight and improved glycemic outcomes in individuals with obesity, with or without type 2 diabetes (39,40). Retatrutide, in turn, by activating GLP-1, GIP, and glucagon receptors, demonstrated promising results in a phase 2 study, suggesting that simultaneous stimulation of multiple hormone receptors may produce a greater metabolic impact (41). These findings indicate a shift in paradigm: peptide-based therapy for obesity is moving away from focusing on a single pathway and advancing toward integrated interventions targeting satiety, insulin secretion, energy expenditure, and hepatic metabolism.

Meanwhile, even among peptide drugs with robust clinical evidence, relevant questions remain. The maintenance of effects appears to depend on ongoing therapy, as observed in studies with semaglutide (37). In addition, long-term data are still needed on safety, adherence, individual response, maintenance of lean mass, expanded cardiometabolic effects, and the impact after discontinuation. Cost, access, and the need for clinical follow-up are also relevant aspects for implementing these therapies at scale. Thus, although incretin agonists represent a substantial advance, their incorporation

should be accompanied by strategies for comprehensive patient monitoring and management.

Mitochondrial peptides and regulators of energy homeostasis, such as MOTS-c and adropin, add an innovative perspective to the discussion. MOTS-c has been shown to improve metabolic homeostasis, reduce obesity, and attenuate insulin resistance in experimental models (42). In humans, the association between plasma MOTS-c and insulin sensitivity in lean individuals suggests translational relevance, although the lack of this association in obese individuals indicates possible resistance, regulatory dysfunction, or alteration of the mitochondrial axis in compromised metabolic states (43). Adropin, in turn, has been associated with energy homeostasis, lipid metabolism, and substrate oxidation preference in muscle (44,45). These findings expand the field of metabolic peptides beyond classical intestinal and hormonal regulation, incorporating mechanisms related to mitochondrial function and metabolic flexibility.

The integration of the results suggests that bioactive peptides exert metabolic effects across three major dimensions. The first involves the digestive and incretin dimension, characterized by DPP-IV inhibition, modulation of GLP-1/GIP secretion, and possible control of postprandial glycemia. The second involves the cellular and inflammatory dimension, marked by improved insulin signaling, activation of Akt/AMPK, and reduced metabolic inflammation. The third involves the neuroendocrine and energy dimension, consisting of effects on satiety, food intake, energy expenditure, substrate oxidation, and mitochondrial function. This integrated approach helps explain why peptides may have simultaneous effects on body weight, glycemia, and insulin sensitivity.

A relevant contribution of this review is to demonstrate that bioactive peptides should be understood within a translational continuum. At one end, there are food-derived peptides and protein hydrolysates with evidence predominantly experimental, but with high potential for the development of functional foods, nutraceuticals, or adjuvant compounds. At the other end are already established or emerging peptide drugs, such as liraglutide, semaglutide,

tirzepatide, and retatrutide, with robust clinical evidence and direct use in obesity and type 2 diabetes. Between these poles are gastrointestinal peptides, hormone analogs, and mitochondrial peptides, which have relevance both physiologically and therapeutically.

The limitations of this review should be considered. The main limitation arises from the heterogeneity of the included studies, which varied in methodological design, type of peptide, dose, route of administration, population, experimental model, intervention time, and outcomes assessed. This heterogeneity prevented the performance of a quantitative meta-analysis and required a qualitative synthesis of the findings. In addition, a significant portion of studies with food peptides was conducted in in vitro or animal models, reducing the strength of clinical inference. Another relevant point is that clinical studies with peptide drugs generally show greater methodological rigor, structured funding, and larger samples, which may lead to an imbalance when comparing with nutritional and experimental studies.

Despite these limitations, the results have important implications for research and clinical practice. In the research field, there is a need for well-designed clinical trials evaluating specific food peptides, standardized doses, bioavailability, Safety and efficacy in individuals with obesity, insulin resistance, or type 2 diabetes. Studies are also needed to investigate the interaction between bioactive peptides, the intestinal microbiota, metabolic inflammation, and individual response. In the clinical field, the results reinforce the value of incretin and multi-agonist peptide therapies, while pointing to the future potential of nutritional and nutraceutical strategies based on bioactive peptides.

Thus, this review shows that bioactive peptides represent a relevant scientific frontier in regulating energy metabolism. While food peptides offer a promising perspective for prevention and metabolic support, hormonal and pharmacological peptides have already demonstrated robust clinical efficacy in the treatment of obesity and type 2 diabetes. The convergence between nutrition, endocrinology, biotechnology, and peptide pharmacology is likely to expand

therapeutic possibilities for weight control, improved insulin sensitivity, and prevention of metabolic complications.

## CONCLUSION

This systematic review showed that bioactive peptides play a relevant role in the regulation of energy metabolism, in the control of body weight, and in modulating insulin sensitivity, acting through multiple and complementary mechanisms. The analyzed evidence indicates that these molecules can influence digestive, incretin, hormonal, inflammatory, cellular, mitochondrial, and neuroendocrine pathways, reinforcing their importance as metabolic agents of scientific and therapeutic interest.

Dietary bioactive peptides, derived from sources such as soy, egg, milk, quinoa, fish, macroalgae, and protein hydrolysates, showed promising potential for improving glycemic homeostasis, especially through DPP-IV inhibition, modulation of enzymes related to carbohydrate digestion, reduction of metabolic inflammation, and improved insulin signaling. However, most of this evidence is still concentrated in in vitro and preclinical studies, which limits their immediate translation into broad clinical recommendations. Thus, although they represent a relevant area for the development of functional foods, nutraceuticals, and adjuvant strategies, controlled clinical trials are still needed to confirm efficacy, safety, the ideal dose, and applicability in humans.

Gastrointestinal and neurohormonal peptides, such as PYY3-36, oxyntomodulin, and pramlintide, have shown important involvement in the control of satiety, food intake, energy expenditure, and weight reduction. These findings reinforce that control of body weight involves a complex network of hormonal signals, and not just isolated caloric balance. The integrated action of these peptides suggests that combined therapeutic approaches may offer superior benefits, especially when targeted simultaneously to hunger, satiety, energy expenditure, and glycemic control.

Among the interventions with the greatest clinical robustness, GLP-1 receptor agonists stood out, such as liraglutide and semaglutide, as well as dual agonists and incretin triagonists, such as

tirzepatide and retatrutide. These peptide drugs have demonstrated consistent effects on weight loss, improved glycemia, weight maintenance, and metabolic control in individuals with overweight, obesity, and type 2 diabetes. Such results consolidate peptide therapies as one of the main contemporary frontiers in the treatment of obesity and associated metabolic disorders.

Mitochondrial peptides and regulators of energy homeostasis, such as MOTS-c and adropin, broaden the understanding of the role of peptides in metabolism by demonstrating an association with insulin sensitivity, substrate oxidation, lipid metabolism, and metabolic flexibility. Although they are still in a more exploratory stage compared with incretin agonists, these peptides represent a promising field for future investigations into mitochondrial function, insulin resistance, and energy adaptation.

In general, the results of this review indicate that bioactive peptides should be understood as an expanding biological and therapeutic platform, with potential applications ranging from functional nutrition to advanced metabolic pharmacology. The main strength of the clinical evidence currently lies with incretin peptide drugs and multi-agonists, while food- and mitochondrial-derived peptides still require greater translational validation. Therefore, future research should prioritize well-designed clinical trials, dose standardization, assessment of bioavailability, long-term safety, interaction with the gut microbiota, and identification of populations that may benefit more significantly from these interventions.

It is concluded that bioactive peptides represent a promising and scientifically relevant strategy for modulating energy metabolism, weight control, and improving insulin sensitivity. Their integrated action on satiety, blood glucose, inflammation, insulin signaling, and metabolic flexibility positions this class of molecules as one of the most strategic areas for the development of new preventive and therapeutic approaches for obesity, insulin resistance, and type 2 diabetes mellitus.

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