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Growth Hormone Secretagogues: Between Endocrine Physiology and the Therapeutic Frontier of GH-IGF-1 Axis-Modulating Peptides

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Abstract

Growth hormone (GH) plays a central role in the regulation of somatic growth, body composition, energy metabolism, bone homeostasis, and cardiovascular function. Physiological GH secretion is controlled by a complex interplay of hypothalamic factors, primarily growth hormone-releasing hormone (GHRH) and somatostatin, as well as ghrelin and several metabolic and hormonal modulators. Over the past decades, the development of growth hormone secretagogues (GHSs) has significantly expanded the possibilities for pharmacological modulation of the GH-insulin-like growth factor 1 (GH-IGF-1) axis. Growth hormone secretagogues comprise a heterogeneous class of compounds capable of stimulating endogenous GH secretion through activation of the growth hormone secretagogue receptor (GHS-R1a). This group includes synthetic peptides such as GHRP-2, GHRP-6, hexarelin, and ipamorelin, as well as non-peptide molecules such as ibutamoren (MK-677). More recently, novel peptide analogs and combination therapeutic strategies have been developed to optimize the somatotropic response while minimizing off-target effects on other endocrine pathways. This review summarizes the physiological mechanisms regulating the GH-IGF-1 axis, the pharmacological characteristics of the major growth hormone secretagogues currently available, their established and emerging clinical applications, and the current evidence regarding their efficacy and safety. In addition, it discusses future therapeutic perspectives, as well as the regulatory and ethical challenges associated with the use of these compounds in regenerative medicine, healthy aging, and physical perfor-

mance enhancement.

Keywords

Growth Hormone, Growth Hormone Secretagogues, GHRP, GH-IGF-1 Axis, Therapeutic Peptides

1. Introduction

Growth hormone (GH), synthesized and secreted by the somatotroph cells of the anterior pituitary gland, plays a pivotal role in the regulation of somatic growth, body composition, energy metabolism, bone homeostasis, and multiple physiological processes throughout life [1] [2]. Many of its biological effects are mediated by insulin-like growth factor 1 (IGF-1), primarily produced by the liver in response to GH stimulation, thereby constituting the GH-IGF-1 axis, one of the principal neuroendocrine systems governing growth, tissue development, and metabolic homeostasis [1].

GH secretion occurs in a pulsatile manner and is tightly regulated by a complex interaction between stimulatory and inhibitory hypothalamic signals. Growth hormone-releasing hormone (GHRH) stimulates GH synthesis and secretion, whereas somatostatin exerts a potent inhibitory effect on pituitary somatotrophs [3]. The discovery of ghrelin and its specific receptor, the growth hormone secretagogue receptor type 1a (GHS-R1a), significantly advanced the understanding of the physiological regulation of the somatotropic axis by demonstrating that GH secretion is influenced not only by classical hypothalamic mechanisms but also by peripheral signals associated with nutritional status, energy balance, and metabolic homeostasis [4] [5].

The identification of GHS-R1a enabled the development of growth hormone secretagogues (GHSs), a heterogeneous class of compounds capable of stimulating endogenous GH secretion through activation of this receptor. These agents include synthetic peptide secretagogues such as GHRP-2, GHRP-6, hexarelin, and ipamorelin, as well as non-peptide agonists such as ibutamoren (MK-677). More recently, novel GHRH analogs and long-acting secretagogues have been developed to optimize GH secretion while preserving, to varying degrees, the physiological regulation of the GH-IGF-1 axis. These compounds have attracted increasing interest because of their potential therapeutic applications in growth hormone deficiency, disorders of body composition, HIV-associated lipodystrophy, age-related functional decline, and other metabolic conditions [6].

Given these advances, this review provides a comprehensive overview of the physiology of the GH-IGF-1 axis, the molecular and pharmacological mechanisms of the principal growth hormone secretagogues, their established and emerging clinical applications, current evidence regarding efficacy and safety, regulatory considerations, and future perspectives for their use in endocrinology,

metabolic medicine, and regenerative therapeutics.

2. Methodology

This study was conducted as a narrative literature review aimed at summarizing and critically discussing the current scientific evidence regarding the physiology of the GH-IGF-1 axis, the mechanisms of action of growth hormone secretagogues (GHSs), and their established and emerging clinical applications.

A comprehensive literature search was performed in the PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases. Publications in English and Portuguese available through June 2026 were considered. The search strategy employed the following keywords, either individually or in combination, using the Boolean operators AND and OR: *growth hormone secretagogues*, *growth hormone-releasing peptides*, *GHRP*, *ghrelin*, *GHS-R1a*, *growth hormone deficiency*, *IGF-1*, *ibutamoren*, *MK-677*, *ipamorelin*, *sermorelin*, *tesamorelin*, *CJC-1295*, *aging*, *sarcopenia*, and *growth hormone therapy*.

Eligible publications included original research articles, randomized clinical trials, observational studies, experimental investigations, narrative and systematic reviews, meta-analyses, expert consensus statements, clinical practice guidelines, and regulatory documents addressing the physiological, pharmacological, therapeutic, or safety aspects of growth hormone secretagogues. Studies were selected based on scientific relevance, methodological quality, recency, and their contribution to the understanding of the topic.

As a narrative review, this study did not follow a predefined systematic review protocol, nor were formal risk-of-bias assessments or quantitative meta-analyses performed. Instead, the selected literature was analyzed through a critical and interpretative approach, allowing the integration of evidence from different study designs and providing a comprehensive overview of the current knowledge on growth hormone secretagogues.

The retrieved evidence was organized into thematic sections covering the physiology of the GH-IGF-1 axis, the discovery and classification of growth hormone secretagogues, peptide and non-peptide compounds, molecular mechanisms of action, established and emerging clinical applications, efficacy and safety, regulatory and ethical considerations, and future perspectives for the use of these agents in endocrinology, metabolic medicine, and regenerative therapeutics.

Because this review was based exclusively on data obtained from previously published scientific literature and did not involve human participants, animals, or identifiable personal data, approval by an Institutional Review Board or Research Ethics Committee was not required, in accordance with international guidelines governing literature review studies.

3. Physiology of the GH-IGF-1 Axis

The growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis is one of the principal neuroendocrine systems responsible for regulating somatic growth, tis-

sue development, body composition, energy metabolism, and metabolic homeostasis throughout life. Its activity results from the coordinated interaction of hypothalamic, pituitary, and peripheral regulatory mechanisms that precisely control the synthesis, pulsatile secretion, and biological actions of growth hormone (GH) [7].

GH is synthesized and secreted by the somatotroph cells of the anterior pituitary gland in a pulsatile pattern that is influenced by several physiological factors, including age, sex, sleep architecture, physical exercise, nutritional status, and metabolic conditions. The central regulation of GH secretion depends primarily on the balance between two hypothalamic hormones: growth hormone-releasing hormone (GHRH), which stimulates GH synthesis and secretion, and somatostatin, which exerts a potent inhibitory effect on pituitary somatotrophs [7].

The discovery of ghrelin represented a major advance in the understanding of the physiology of the GH-IGF-1 axis. Produced predominantly by oxyntic cells of the gastric mucosa, ghrelin acts as the endogenous ligand for the growth hormone secretagogue receptor type 1a (GHS-R1a), which is expressed in both the hypothalamus and the anterior pituitary. Activation of this receptor stimulates pulsatile GH secretion while also regulating appetite, energy balance, glucose homeostasis, and whole-body metabolism, thereby establishing an important physiological link between nutritional status and somatotropic function [7] [8].

Following its release into the systemic circulation, GH exerts direct effects on multiple target tissues, including skeletal muscle, adipose tissue, liver, and bone. In addition to these direct actions, GH stimulates hepatic synthesis of insulin-like growth factor 1 (IGF-1), the principal mediator of the anabolic and growth-promoting effects of the somatotropic axis. IGF-1 acts through endocrine, paracrine, and autocrine mechanisms to promote cell proliferation, tissue differentiation, protein synthesis, and the maintenance of skeletal muscle and bone mass [9].

Homeostasis of the GH-IGF-1 axis is maintained through a sophisticated negative feedback system. Elevated circulating IGF-1 concentrations suppress GH secretion by acting directly on the pituitary gland and indirectly through hypothalamic regulation, increasing somatostatin release while inhibiting GHRH secretion. This feedback mechanism ensures physiological control of somatotroph activity and prevents excessive exposure of peripheral tissues to the proliferative effects of GH and IGF-1 [8] [9].

Beyond the classical hormonal regulators, several metabolic factors—including glucose, amino acids, free fatty acids, insulin, and thyroid hormones—also influence the activity of the GH-IGF-1 axis. Alterations in these regulatory pathways may result in clinically significant disorders, including growth hormone deficiency, GH resistance, and states of GH hypersecretion such as acromegaly [9].

A comprehensive understanding of the physiology and regulatory mechanisms governing the GH-IGF-1 axis has been fundamental to the development of growth hormone secretagogues. These compounds stimulate endogenous GH secretion either through activation of the growth hormone secretagogue receptor (GHS-

R1a) or by enhancing GHRH-mediated signaling, thereby preserving, to varying degrees, the physiological feedback mechanisms of the somatotropic axis and providing the rationale for their therapeutic development in endocrine and metabolic disorders [9].

4. Discovery of Growth Hormone Secretagogues

The development of growth hormone secretagogues (GHSs) represents one of the most significant advances in the understanding of the neuroendocrine regulation of the somatotropic axis. Research leading to the discovery of these compounds began in the late 1970s and expanded during the early 1980s, when investigators sought synthetic peptides capable of stimulating growth hormone (GH) secretion through mechanisms distinct from those mediated by growth hormone-releasing hormone (GHRH), whose physiological role was still being elucidated at that time [10].

In this context, Cyril Y. Bowers and colleagues synthesized a series of synthetic peptides derived from methionine-enkephalin analogs and identified compounds capable of inducing potent and relatively selective GH release. These molecules gave rise to the class of Growth Hormone-Releasing Peptides (GHRPs), with GHRP-6 becoming one of the earliest and most extensively investigated representatives. Their findings demonstrated that these peptides stimulated GH secretion through mechanisms independent of GHRH signaling, suggesting the existence of a previously unidentified regulatory pathway controlling somatotroph function [10].

During the following decades, additional synthetic peptides—including GHRP-2, hexarelin, and ipamorelin—were developed to improve secretagogue potency, receptor selectivity, and pharmacokinetic stability. The pharmacological properties of these compounds provided compelling evidence for the existence of a specific receptor mediating their biological effects, thereby stimulating further investigations aimed at elucidating the molecular mechanisms regulating GH secretion [11].

A major breakthrough occurred in 1996 when Howard and colleagues identified and cloned the growth hormone secretagogue receptor type 1a (GHS-R1a), which is predominantly expressed in the hypothalamus and anterior pituitary gland. The characterization of this receptor confirmed the existence of a novel physiological pathway regulating GH secretion that is functionally distinct from, yet closely integrated with, the classical GHRH and somatostatin signaling pathways. This discovery established the molecular foundation for the rational development of both peptide and non-peptide agonists targeting the ghrelin-GHS-R1a signaling system [11].

A few years later, Kojima and colleagues identified ghrelin, an acylated peptide produced predominantly by oxyntic cells of the gastric mucosa and recognized as the endogenous ligand of GHS-R1a. This landmark discovery transformed the understanding of endocrine regulation by demonstrating that GH secretion is con-

trolled not only by classical hypothalamic mechanisms involving GHRH and somatostatin but also by peripheral signals linked to nutritional status, energy balance, and metabolic homeostasis. In addition to stimulating pulsatile GH secretion, ghrelin was shown to regulate appetite, food intake, and energy metabolism, thereby establishing a functional connection between the gastrointestinal tract and the somatotropic axis [12].

The characterization of the ghrelin-GHS-R1a system provided the physiological and pharmacological basis for the development of a new generation of growth hormone secretagogues, including both peptide and non-peptide agonists such as ibutamoren (MK-677). These compounds substantially expanded the therapeutic possibilities for pharmacological modulation of the GH-IGF-1 axis and have been investigated for potential applications in growth hormone deficiency, sarcopenia, age-related frailty, disorders of body composition, and other metabolic conditions. Although several agents have demonstrated promising pharmacological and clinical effects, their long-term efficacy and safety continue to be evaluated in ongoing preclinical and clinical studies [13].

5. Classification of Growth Hormone Secretagogues

Growth hormone secretagogues (GHSs) comprise a heterogeneous group of compounds capable of stimulating endogenous growth hormone (GH) secretion through the modulation of different components of the somatotropic axis. Based on their chemical structure and mechanism of action, these agents can be broadly classified into two major categories: peptide secretagogues and non-peptide secretagogues [14].

In addition to their structural classification, growth hormone secretagogues can also be functionally categorized as growth hormone secretagogue receptor (GHS-R1a) agonists and growth hormone-releasing hormone (GHRH) analogs. Although both classes increase GH secretion, they act through distinct physiological pathways. GHS-R1a agonists primarily mimic the biological actions of ghrelin by directly activating receptors expressed in the hypothalamus and anterior pituitary, whereas GHRH analogs stimulate pituitary somatotrophs through the physiological GHRH receptor. Because these signaling pathways are complementary, combined administration frequently produces synergistic effects on pulsatile GH secretion and subsequent IGF-1 production while maintaining, to varying degrees, the physiological regulation of the GH-IGF-1 axis [15].

5.1. Peptide Growth Hormone Secretagogues

Peptide growth hormone secretagogues represent the earliest and most extensively investigated class of compounds designed to stimulate the GH-IGF-1 axis. These molecules consist of specific amino acid sequences that partially mimic the physiological actions of either ghrelin or growth hormone-releasing hormone (GHRH), thereby promoting endogenous GH secretion through activation of GHS-R1a or direct stimulation of pituitary somatotroph cells. Owing to their pep-

tide structure, they exhibit limited gastrointestinal stability and poor oral bioavailability, requiring administration predominantly by subcutaneous or intravenous injection [16].

The development of growth hormone-releasing peptides (GHRPs) significantly advanced the understanding of the regulatory mechanisms governing the somatotropic axis and fostered the development of therapeutic strategies aimed at enhancing endogenous GH secretion. Acting as agonists of GHS-R1a, these compounds stimulate pulsatile GH release through direct activation of receptors located in both the hypothalamus and anterior pituitary gland. Compared with exogenous recombinant GH therapy, peptide secretagogues preserve the physiological feedback regulation of the GH-IGF-1 axis to a greater extent, thereby providing a more physiological approach to somatotropic stimulation. Although many peptide secretagogues have demonstrated promising pharmacological and clinical effects in experimental and early clinical studies, their therapeutic applicability varies according to the specific compound, indication, and quality of the available clinical evidence [17].

Among the principal representatives of this class are:

GHRP-2: A synthetic agonist of the growth hormone secretagogue receptor (GHS-R1a) characterized by high secretagogue potency, capable of producing significant increases in circulating GH and IGF-1 concentrations. GHRP-2 has demonstrated consistent stimulation of GH secretion even in individuals with partially impaired somatotropic function [17].

GHRP-6: One of the earliest and most extensively studied growth hormone-releasing peptides. In addition to stimulating GH secretion, GHRP-6 exerts a marked orexigenic effect by activating physiological ghrelin signaling pathways, thereby increasing appetite and food intake [18].

Hexarelin: A synthetic hexapeptide with high affinity for GHS-R1a, recognized for its potent GH-releasing activity and increased resistance to enzymatic degradation. Experimental studies have also suggested potential cardioprotective effects that appear to be partially independent of GH secretion, although their clinical significance remains under investigation [18].

Ipamorelin: A highly selective GHS-R1a agonist developed to minimize stimulation of other endocrine axes. Unlike earlier GHRPs, ipamorelin has minimal effects on the secretion of adrenocorticotropic hormone (ACTH), cortisol, and prolactin, contributing to a more selective pharmacological profile and potentially improved tolerability [17] [18].

Sermorelin: A synthetic peptide corresponding to the biologically active N-terminal 29-amino acid sequence of growth hormone-releasing hormone (GHRH 1-29). It was one of the first GHRH analogs introduced into clinical practice for the diagnosis and treatment of growth hormone deficiency, acting through the physiological stimulation of pituitary somatotroph cells. Unlike GHS-R1a agonists, sermorelin preserves the physiological feedback mechanisms of the hypothalamic-pituitary axis, promoting pulsatile GH secretion in a manner that closely

resembles normal physiology. Although its relatively short half-life has led to its replacement by more stable and longer-acting analogs in most clinical settings, sermorelin played a pivotal role in the development of modern GH secretagogues and continues to be used in selected clinical applications and research protocols evaluating somatotropic function [19].

Tesamorelin: A stabilized synthetic analog of growth hormone-releasing hormone (GHRH) engineered to increase resistance to enzymatic degradation and prolong biological activity. By selectively activating GHRH receptors on anterior pituitary somatotrophs, tesamorelin promotes sustained pulsatile GH secretion and increased hepatic IGF-1 production. Randomized clinical trials have demonstrated significant reductions in visceral adipose tissue in patients with HIV-associated lipodystrophy, leading to its regulatory approval for this specific indication. To date, tesamorelin remains the only GHRH analog with an established therapeutic indication approved for clinical use [20].

CJC-1295: A long-acting GHRH analog designed to extend plasma half-life through reversible binding to serum albumin, thereby providing prolonged stimulation of pituitary somatotroph cells. Clinical studies have demonstrated sustained increases in circulating GH and IGF-1 concentrations while preserving the physiological pulsatile pattern of GH secretion. Its use remains primarily investigational, and it has frequently been evaluated in combination with GHS-R1a agonists because of their potential synergistic effects on endogenous GH secretion [21].

Collectively, GHRH analogs and GHS-R1a agonists constitute the two principal classes of growth hormone secretagogues. Beyond their contribution to understanding the regulatory mechanisms of the GH-IGF-1 axis, these compounds have demonstrated established clinical utility in selected indications, most notably the use of tesamorelin for HIV-associated lipodystrophy. In addition, they continue to be investigated as therapeutic strategies for enhancing endogenous GH secretion in conditions characterized by growth hormone deficiency, impaired somatotropic function, age-related decline in GH secretion, and alterations in body composition and metabolic homeostasis [21].

5.2. Non-Peptide Growth Hormone Secretagogues

Ibutamoren (MK-677), also known as L-163,191, is a selective, orally active, non-peptide agonist of the growth hormone secretagogue receptor (GHS-R1a). Developed during the 1990s as an alternative to injectable peptide secretagogues, ibutamoren was designed to mimic the physiological actions of ghrelin, thereby promoting sustained stimulation of endogenous growth hormone (GH) secretion and increasing circulating insulin-like growth factor 1 (IGF-1) concentrations [22].

Unlike conventional peptide secretagogues, MK-677 exhibits excellent oral bioavailability and a prolonged elimination half-life, allowing once-daily administration. Clinical studies have demonstrated that chronic treatment with MK-677

significantly increases serum GH and IGF-1 concentrations to levels comparable to those observed in healthy young adults while largely preserving the physiological pulsatile pattern of GH secretion [23].

In older adults, prolonged administration of MK-677 has been associated with increases in lean body mass, improvements in nitrogen balance, enhancement of bone mineral density, and partial attenuation of age-related muscle loss. Additional studies have suggested beneficial effects on sleep quality, tissue recovery, and protein metabolism; however, these findings remain heterogeneous across different study populations and have not consistently translated into clinically meaningful improvements in physical function or muscle strength [22] [23].

Despite these promising findings, the clinical use of MK-677 remains limited by the absence of regulatory approval for therapeutic indications. Furthermore, chronic activation of the ghrelin-GHS-R1a signaling pathway has been associated with increased appetite, fluid retention, peripheral edema, arthralgia, reduced insulin sensitivity, and disturbances in glucose metabolism. These observations underscore the need for long-term clinical studies to better define the metabolic and cardiovascular safety profile of this compound before broader therapeutic applications can be considered [24].

5.3. Emerging Molecules

Advances in the molecular pharmacology of GHS-R1a have driven the development of a new generation of non-peptide growth hormone secretagogues aimed at improving oral bioavailability, extending duration of action, and optimizing pharmacokinetic properties while maintaining effective stimulation of the GH–IGF-1 axis. Despite these advances, many of these compounds continue to exhibit physiological effects characteristic of ghrelin receptor activation, including increased appetite and metabolic alterations [25].

Among the most extensively investigated agents are macimorelin and capromorelin. Macimorelin was initially developed as an orally active GHS-R1a agonist and subsequently demonstrated high diagnostic accuracy for adult growth hormone deficiency. These findings led to its regulatory approval as an oral functional diagnostic test for evaluating the somatotropic axis, offering a practical and well-tolerated alternative to conventional GH stimulation tests [26].

Capromorelin has shown promising effects on energy metabolism, appetite stimulation, and lean body mass in experimental and clinical studies. Although its current clinical use is limited to veterinary medicine, it has contributed substantially to the understanding of ghrelin receptor pharmacology and the therapeutic potential of orally active GHS-R1a agonists.

In parallel, several selective GHS-R1a agonists, biased agonists, and allosteric modulators are currently undergoing preclinical and early-phase clinical investigation. These next-generation compounds aim to selectively activate intracellular signaling pathways associated with GH secretion while minimizing undesirable metabolic effects, thereby representing promising candidates for future therapeutic applications in sarcopenia, age-related frailty, cachexia, and other catabolic dis-

orders. Nevertheless, their long-term efficacy, safety, and clinical utility remain to be established through adequately powered randomized clinical trials [26].

6. Current Clinical Applications

The development of growth hormone secretagogues (GHSs) has substantially expanded the therapeutic possibilities for pharmacological modulation of the GH-IGF-1 axis. Although many compounds remain under clinical investigation, a limited number have achieved regulatory approval for specific clinical indications, particularly in the diagnosis of adult growth hormone deficiency and selected therapeutic conditions, whereas most agents continue to be restricted to experimental or investigational use [27].

6.1. Growth Hormone Deficiency

Growth hormone secretagogues were developed as a pharmacological strategy to stimulate endogenous GH secretion while preserving, to a greater extent than exogenous recombinant GH therapy, the physiological pulsatile dynamics and feedback regulation of the GH-IGF-1 axis. By activating either the growth hormone secretagogue receptor (GHS-R1a) or the growth hormone-releasing hormone (GHRH) receptor, these agents promote physiological GH release that remains dependent on the functional integrity of the hypothalamic-pituitary axis.

However, their therapeutic efficacy is largely contingent upon preserved pituitary somatotroph function and adequate hypothalamic regulation. Consequently, in patients with established or severe growth hormone deficiency, particularly those with structural hypothalamic or pituitary disease, the response to secretagogues may be limited. Current evidence has not demonstrated superiority of growth hormone secretagogues over conventional recombinant human GH replacement therapy in terms of efficacy, long-term clinical outcomes, or restoration of physiological endocrine function. Therefore, recombinant human GH remains the standard first-line treatment for confirmed growth hormone deficiency, whereas secretagogues continue to be investigated as potential therapeutic alternatives in carefully selected patient populations or in conditions characterized by partial impairment of the somatotropic axis [28].

6.2. Diagnostic Evaluation of the Somatotropic Axis

The most firmly established clinical application of growth hormone secretagogues is the diagnosis of adult growth hormone deficiency. Among the available agents, macimorelin, an orally active GHS-R1a agonist, has been approved as a functional diagnostic test because of its high sensitivity, specificity, favorable safety profile, and ease of administration compared with traditional provocative tests such as the insulin tolerance test (ITT). In addition to avoiding the risks associated with insulin-induced hypoglycemia, the macimorelin stimulation test offers greater patient convenience, requires less intensive clinical monitoring, and has demonstrated excellent diagnostic agreement with established reference methods in mul-

ticenter clinical trials. These advantages have led to its incorporation into contemporary diagnostic algorithms for the evaluation of adult growth hormone deficiency in appropriately selected patients [29].

6.3. HIV-Associated Lipodystrophy

Tesamorelin represents the most well-established clinical application of a growth hormone-releasing hormone (GHRH) analog. Randomized controlled trials have demonstrated that tesamorelin administration significantly reduces visceral adipose tissue in individuals with HIV-associated lipodystrophy, while also improving metabolic parameters, including reductions in triglyceride levels and hepatic fat content, without compromising virological control. These findings supported its regulatory approval for this specific indication, making tesamorelin, to date, the only growth hormone secretagogue with a broadly established therapeutic indication for the management of HIV-associated lipodystrophy [30].

6.4. Sarcopenia and Age-Related Frailty

Clinical studies evaluating MK-677 (ibutamoren) and other growth hormone secretagogues have demonstrated sustained increases in circulating GH and IGF-1 concentrations, accompanied by favorable changes in body composition, particularly increases in lean body mass and reductions in protein catabolism. However, these biological and structural effects have not consistently translated into clinically meaningful improvements in muscle strength, physical performance, mobility, or frailty-related outcomes. Consequently, the current body of evidence remains insufficient to support the routine use of growth hormone secretagogues for the prevention or treatment of sarcopenia or for promoting healthy aging outside the setting of controlled clinical research [31].

6.5. Cachexia and Catabolic Disorders

Diseases characterized by progressive loss of skeletal muscle mass and cachexia represent another area of interest for growth hormone secretagogues. Advanced malignancies, chronic heart failure, chronic obstructive pulmonary disease (COPD), and other chronic inflammatory disorders have been investigated because of the potential of these agents to stimulate the GH-IGF-1 axis, improve protein anabolism, and favorably modify body composition. Although several studies have reported increases in lean body mass and improvements in selected metabolic parameters, convincing evidence demonstrating meaningful benefits in functional capacity, quality of life, morbidity, or survival remains limited. Consequently, the routine clinical use of growth hormone secretagogues for cachexia and chronic catabolic conditions cannot currently be recommended outside research settings [32].

6.6. Metabolic Recovery and Regenerative Medicine

The anabolic properties of growth hormone secretagogues have also generated

considerable interest in applications related to metabolic recovery, tissue repair, wound healing, and regenerative medicine. By stimulating endogenous GH secretion and increasing IGF-1 production, these agents may promote protein synthesis, skeletal muscle regeneration, bone remodeling, collagen formation, and tissue repair. Nevertheless, most of the available evidence derives from experimental studies, animal models, or small-scale clinical investigations with heterogeneous methodologies and limited demonstration of consistent clinical benefit. At present, there is no scientific consensus or recommendation from international clinical guidelines supporting the routine use of growth hormone secretagogues for regenerative medicine, enhancement of tissue healing, or acceleration of recovery processes. Further well-designed randomized clinical trials are required to establish their efficacy, long-term safety, and therapeutic role in these emerging applications [33].

7. Safety, Adverse Effects, and Limitations

Despite the growing clinical and scientific interest in growth hormone secretagogues (GHSs), their long-term safety remains one of the principal barriers to their widespread incorporation into clinical practice. Although these agents stimulate endogenous GH secretion in a manner that more closely resembles physiological regulation and partially preserves the natural feedback mechanisms of the GH-IGF-1 axis, prolonged administration may result in adverse effects associated with sustained activation of the somatotropic axis and chronic stimulation of the growth hormone secretagogue receptor (GHS-R1a) [34].

The most frequently reported adverse events include fluid retention, peripheral edema, weight gain, headache, arthralgia, myalgia, and paresthesia. These manifestations are comparable to those observed during recombinant human growth hormone therapy and are thought to result primarily from increased anabolic activity, enhanced sodium retention, and alterations in extracellular fluid balance induced by activation of the GH–IGF-1 axis [34].

Metabolic disturbances also represent an important safety concern. Clinical studies evaluating GHS-R1a agonists, particularly ibutamoren (MK-677), have demonstrated transient increases in insulin resistance, elevations in fasting plasma glucose, and reduced peripheral insulin sensitivity in some individuals, especially those with pre-existing metabolic risk factors or impaired glucose tolerance. These findings highlight the importance of careful metabolic monitoring during prolonged treatment and underscore the need for further investigation into the long-term metabolic consequences of chronic GHS-R1a activation [34] [35].

Another important consideration relates to the potential proliferative effects of sustained IGF-1 elevation. Although current clinical evidence does not demonstrate an increased incidence of malignancy associated with the therapeutic use of growth hormone secretagogues, persistently elevated circulating concentrations of GH and IGF-1 have been associated in epidemiological and experimental studies with enhanced mitogenic and anti-apoptotic signaling. Consequently, caution

is warranted when considering these agents in individuals with a personal or family history of hormone-sensitive malignancies or other conditions associated with increased cancer risk [36] [37].

In addition to safety concerns, several methodological limitations continue to restrict the interpretation of the available evidence. Most clinical studies have involved relatively small sample sizes, short follow-up periods, heterogeneous patient populations, and variability in treatment regimens and outcome measures. Furthermore, only a limited number of randomized controlled trials have evaluated clinically meaningful endpoints such as physical function, quality of life, cardiovascular outcomes, or long-term mortality. These limitations preclude definitive conclusions regarding the efficacy and long-term safety of growth hormone secretagogues and reinforce the need for larger, well-designed clinical trials with extended follow-up before broader therapeutic recommendations can be established [38].

8. Regulatory and Ethical Considerations

The regulatory status of growth hormone secretagogues (GHSs) varies considerably among countries and regulatory agencies. To date, only a limited number of these compounds have received formal approval for specific clinical indications. Tesamorelin has been approved for the treatment of HIV-associated lipodystrophy, whereas macimorelin has been approved as an oral diagnostic test for adult growth hormone deficiency, based on clinical evidence demonstrating its diagnostic accuracy, safety, and practicality [39].

In contrast, most peptide secretagogues widely promoted in anti-aging, hormone optimization, and wellness settings—including GHRP-2, GHRP-6, hexarelin, ipamorelin, and CJC-1295—have not received regulatory approval for routine therapeutic use in most countries. These compounds are frequently marketed as research chemicals or laboratory reagents rather than approved pharmaceutical products, and their clinical use remains unsupported by robust evidence regarding long-term efficacy and safety [40].

The use of growth hormone secretagogues for aesthetic purposes, enhancement of athletic performance, or longevity interventions raises important ethical concerns. The widespread promotion of these compounds despite the limited availability of high-quality long-term clinical evidence poses significant challenges for evidence-based medical practice and patient safety. Healthcare professionals must carefully balance the potential therapeutic benefits of these agents against the uncertainties regarding their long-term safety profile, while ensuring that patients receive accurate information regarding their approved indications and current level of scientific evidence [41].

In the field of competitive sports, several growth hormone secretagogues and modulators of the GH-IGF-1 axis are classified as prohibited substances by the World Anti-Doping Agency (WADA) under the category of Peptide Hormones, Growth Factors, Related Substances and Mimetics (S2). This category includes growth hormone, GHRH analogs, GHS-R1a agonists, and other GH secreta-

gogues because of their potential to alter body composition, stimulate anabolic pathways, and enhance physical performance. The detection of these compounds continues to present significant challenges for anti-doping laboratories owing to the structural diversity of available agents, the continuous emergence of novel analogs, and the relatively short detection windows of some substances. Consequently, the development of increasingly sensitive analytical methods remains a priority for preserving fairness and integrity in competitive sports [42].

9. Future Perspectives

Rapid advances in molecular biology, peptide engineering, and the pharmacology of G protein-coupled receptors have accelerated the development of next-generation growth hormone secretagogues with greater pharmacological selectivity and improved control of the pleiotropic effects associated with activation of the ghrelin-GHS-R1a signaling pathway. Contemporary drug development strategies extend beyond simply increasing GH secretion and instead focus on the selective modulation of intracellular signaling pathways to maximize therapeutic efficacy while minimizing undesirable metabolic and cardiovascular effects [42].

One of the most promising areas of research involves the development of selective agonists and allosteric modulators of GHS-R1a capable of inducing specific biological responses through the concept of biased signaling. This pharmacological approach aims to preferentially activate intracellular signaling pathways responsible for the desired anabolic and somatotropic effects while minimizing activation of pathways associated with adverse metabolic consequences. Although experimental studies have demonstrated encouraging results, the clinical translation of biased GHS-R1a signaling remains in its early stages and requires further investigation before therapeutic applications can be established [43].

Additional research is also focusing on long-acting GHRH analogs, orally active non-peptide agonists with improved pharmacokinetic profiles, combination therapies targeting complementary regulatory pathways of the GH-IGF-1 axis, and precision medicine strategies based on individual endocrine and metabolic characteristics. These approaches may expand the therapeutic potential of growth hormone secretagogues in conditions such as sarcopenia, frailty, cachexia, metabolic disorders, and selected endocrine diseases.

Nevertheless, the successful clinical implementation of these emerging therapies will depend on the availability of large, multicenter, randomized clinical trials with long-term follow-up capable of evaluating clinically meaningful outcomes, including mortality, cardiovascular safety, metabolic health, cancer risk, physical function, and quality of life. Only through robust evidence generated by such studies will it be possible to define the appropriate role of growth hormone secretagogues in future endocrine and metabolic medicine.

10. Conclusions

Growth hormone secretagogues (GHSs) represent one of the most significant ad-

vances in the understanding and pharmacological modulation of the GH-IGF-1 axis over the past several decades. The discovery of the ghrelin-GHS-R1a signaling system provided the foundation for the development of compounds capable of stimulating endogenous GH secretion in a manner that more closely resembles physiological regulation than conventional recombinant growth hormone replacement therapy, thereby expanding the therapeutic possibilities for modulating the somatotropic axis.

Over the years, multiple classes of growth hormone secretagogues, including synthetic peptide analogs and orally active non-peptide agonists, have demonstrated the ability to increase circulating GH and IGF-1 concentrations, with potential benefits for body composition, protein metabolism, musculoskeletal function, and overall metabolic homeostasis. Some of these compounds have achieved well-established clinical applications, most notably tesamorelin for the treatment of HIV-associated lipodystrophy and macimorelin as an oral diagnostic test for adult growth hormone deficiency.

Nevertheless, despite encouraging findings from experimental and clinical studies, many of the proposed therapeutic applications of growth hormone secretagogues—particularly in the fields of healthy aging, regenerative medicine, metabolic optimization, and age-related frailty—remain supported by limited clinical evidence. Current data are insufficient to justify their routine clinical use for these indications, and important questions regarding long-term safety, metabolic effects, cardiovascular outcomes, oncological risk, and the consequences of chronic activation of the GH-IGF-1 axis remain unresolved.

Future progress in this field will depend on the completion of large, multicenter, randomized clinical trials with extended follow-up that are capable of establishing the efficacy, safety, and long-term clinical impact of these agents. In addition, advances in receptor pharmacology, peptide engineering, and biased GHS-R1a signaling may facilitate the development of next-generation secretagogues with improved selectivity, enhanced safety profiles, and more favorable therapeutic indices. As these innovations evolve, growth hormone secretagogues are expected to play an increasingly important role in endocrinology, metabolic medicine, and precision therapeutic strategies aimed at preserving functional capacity, metabolic health, and quality of life throughout aging.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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