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Study of long-acting vs daily growth hormone: peak levels, AUC, action duration, and IGF-1

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Abstract

Introduction: Long-acting growth hormone (LAGH) therapy was developed to improve adherence by reducing injection frequency compared to daily growth hormone (GH) therapy. Objectives: This review assesses the impact of LAGH therapy on serum levels of GH and insulin-like growth factor-1 (IGF-1) and evaluates the potential metabolic and safety risks compared to the natural pulsatile secretion of GH and daily GH injections in normal children. Methods: A comprehensive literature search identified studies examining the effects of LAGH therapy on serum GH and IGF-1 levels. Results: Studies from 2010 to 2024 were included. LAGH formulations maintain elevated IGF-1 levels for extended periods, in contrast to the episodic peaks and troughs of natural GH secretion. These formulations demonstrate efficacy in promoting growth and maintaining IGF-1 levels but are associated with sustained nonpulsatile GH exposure. Significant intra- and interindividual variability in GH uptake after injection has been observed, with higher GH concentrations correlating with increased IGF-1 levels and growth response. Concerns have been raised about adverse metabolic outcomes, including decreased insulin sensitivity. Sustained high IGF-1 levels with LAGH therapy may also increase risks for certain cancers and proliferative disorders, although evidence remains inconclusive. Discussion: While LAGH therapy offers improved adherence, it leads to nonphysiological, sustained high levels of GH and IGF-1, raising concerns about long-term metabolic effects. Conclusions: LAGH therapy presents a viable alternative to daily GH injections, providing improved adherence and convenience. However, continuous monitoring of long-term metabolic and safety risks and performing long-term studies are crucial to ensuring safe and effective use in clinical practice.

Keywords: *long-acting growth hormone*, *insulin-like growth factor-1 levels*, *growth hormone pulsatility*, *metabolic risks*, *insulin sensitivity*, *safety profile*

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1. Introduction

Long-acting growth hormone (LAGH) analogs have been developed to improve adherence to growth hormone (GH) therapy by reducing the frequency of injections compared to daily recombinant human growth hormone (rhGH) administration. Regarding the LAGH formulations, several forms have been developed by increasing the effective size of rhGH and reducing its rate of clearance from the body, such as Fc-fusion rhGH and polyethylene glycated (PEGylated) recombinant human growth hormone (PEG-rhGH). While LAGH analogs are anticipated to share many of the known side effects of daily rhGH, the mechanism by which GH action is prolonged and the duration of its prolongation may introduce additional safety risks. One of the primary concerns is the altered profile of serum GH and insulin-like growth factor-1 (IGF-1) levels during therapy with LAGH analogs [1–3].

A significant pitfall of LAGH analogs is the impact of prolonged elevated serum GH levels following an injection. This results in a relative lack of the natural daily GH nocturnal peak and daytime trough profile, which is mimicked by daily rhGH injections administered at bedtime. This disruption of the physiological pulsatile secretion pattern of GH may have metabolic consequences. Continuous exposure to elevated GH levels can affect the regulation of fat and glucose metabolism and body composition, potentially leading to long-term metabolic aberrations [1, 2].

Furthermore, the low levels of GH prior to the next LAGH injection may pose a risk, particularly for infants and young children with severe growth hormone deficiency (GHD), who are prone to hypoglycemia. The lack of consistent GH levels could exacerbate this risk, placing these vulnerable populations at unnecessary risk [1– 3].

Given these concerns, the literature on the metabolic and safety profiles of LAGH analogs compared to daily GH therapy needs thorough examination. Christiansen et al. [1] emphasized the need for long-term surveillance to understand the full spectrum of safety and efficacy of LAGH compounds, especially concerning their unique pharmacodynamic properties. Additionally, Hoybye and

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Christiansen [2] and Johannsson [3] have discussed the potential metabolic impacts of altered GH and IGF-1 profiles associated with LAGH therapy. Studies have shown that prolonged exposure to elevated GH and IGF-1 levels can disrupt normal metabolic processes. For example, continuous GH exposure has been associated with insulin resistance and impaired glucose metabolism, which can lead to an increased risk of diabetes [4, 5]. Additionally, elevated IGF-1 levels have been linked to an increased risk of certain cancers, highlighting the need for careful monitoring and risk assessment in patients undergoing LAGH therapy [6, 7].

This review aims to elucidate the effects of LAGH therapy on serum GH and IGF-1 levels, comparing these effects to the physiological pulsatile GH secretion observed in healthy individuals and the profiles achieved with daily GH injections. By examining the current literature, we seek to clarify the extent of these altered profiles and their potential long-term metabolic and safety implications.

2. Methods

2.1. Literature search

A comprehensive literature search was conducted to identify studies investigating the effects of LAGH therapy on serum GH and IGF-1 levels, with a particular focus on comparing these effects to physiological pulsatile GH secretion and daily GH injections. The following electronic databases were searched: PubMed, Embase, Web of Science, and Cochrane Library. Search terms included "long-acting growth hormone", "LAGH", "serum GH levels", "IGF-1 levels", "pulsatile GH secretion", and "daily GH injections". The search was limited to articles published in English from January 2000 to December 2023 (**Figure 1**).

2.2. Inclusion and exclusion criteria

Studies were included if they:

1. Investigated the effects of LAGH therapy on serum GH and IGF-1 levels.
2. Compared these effects with either the physiological pulsatile GH secretion or daily GH injections.
3. Included both children and adult populations with GHD.
4. Provided sufficient data on GH and IGF-1 serum levels and safety outcomes.
5. Were animal studies.

Studies were excluded if they:

1. Were not published in English.
2. Did not provide clear data on GH and IGF-1 levels.
3. Were case reports, reviews, editorials, or conference abstracts without original data.
4. Focused on populations with conditions other than GHD.

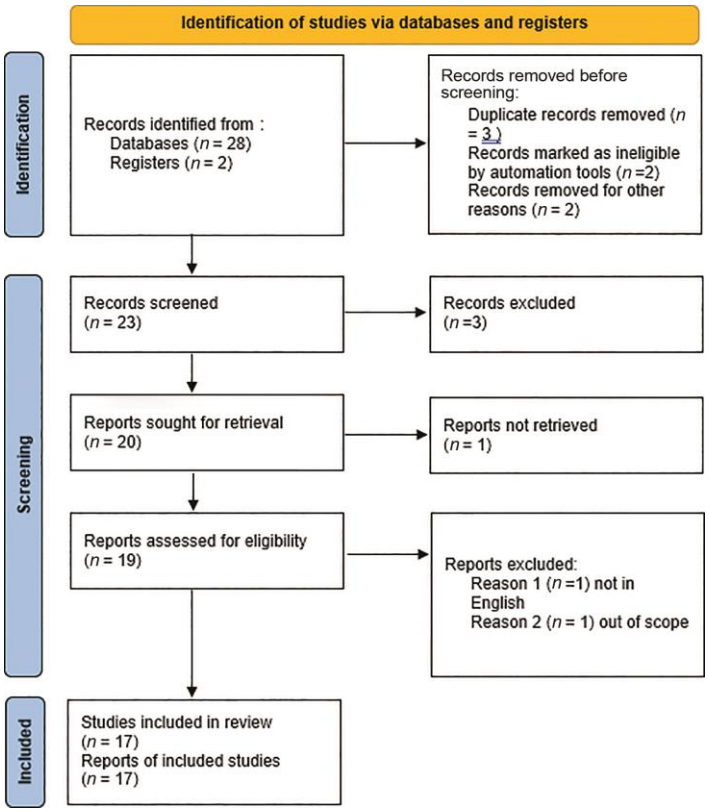

Figure 1 • PRISMA characteristics of the study (flow diagram).

2.3. Data extraction

Data from the included studies were extracted independently by two reviewers using a standardized form. The extracted data included:

- Study characteristics: authors, year of publication, and journal.
- Population characteristics: age, sex, and sample size.
- Intervention details: type of LAGH, dosage, and frequency of administration.
- Outcomes: serum GH and IGF-1 levels, safety profiles, and any reported adverse events.

2.4. Data synthesis and analysis

Extracted data were synthesized to compare the effects of LAGH therapy on serum GH and IGF-1 levels with those of physiological pulsatile GH secretion and daily GH injections. The potential risks associated with nonpulsatile GH exposure were also analyzed. Findings were summarized in a narrative format, and key results were presented in tables for clarity.

3. Ethical aspects

This review involved the analysis of data from previously published studies and did not include any new data collection from human participants. Therefore, no ethical approval was required. However, all included studies were assumed to have been conducted in accordance with ethical standards, including obtaining informed consent from participants and approval from relevant ethics committees. The authors of this review adhered to ethical guidelines for reporting research findings, ensuring accuracy, transparency, and integrity in the presentation of the results.

4. Results

The main findings of the research articles analyzed in this review are presented in **Table 1**.

Table 1 • Long-acting growth hormone therapies: efficacy and safety considerations (humans and mice)

Author and year	Main findings
Masternak et al. [8]	GH treatment in Ames dwarf mice inhibited insulin signaling and decreased insulin sensitivity compared to physiological GH secretion.
Spielhagen et al. [9]	Long-term GH replacement in adults with GH deficiency resulted in significant increases in IGF-1 levels without significant changes in cholesterol or BMI.
Johannsson [3]	Long-acting GH therapy may disrupt the natural balance with insulin and affect metabolic processes, indicating the need for careful consideration of safety and efficacy.
Pampanini et al. [10]	Long-acting GH formulations face challenges regarding safety and efficacy, with different pharmacokinetic profiles compared to daily GH injections.
Yuen et al. [11]	Long-acting GH formulations sustain elevated IGF-1 levels and show beneficial effects in adults over the short term, but long-term studies are needed for safety validation.
Kim et al. [12]	The long-acting rhGH–Fc formulation maintained GH levels for a week, providing growth effects comparable to those of daily GH injections.
Christiansen et al. [1]	LAGH compounds offer the potential for improved adherence due to less frequent dosing. However, they present differing pharmacodynamic properties that could affect GH and IGF-1 levels. Long-term surveillance is essential to understand their impact on safety and efficacy. Lonapegsomatropin is a long-acting prodrug of Somatropin that is transiently bound to a carrier via a proprietary TransCon linker.
Zelinska et al. [13]	Weekly MOD-4023 showed long-acting properties with dose-dependent IGF-1 increases and adequate growth in children, comparable to daily GH. MOD-4023 is a LAGH based on C-terminal peptide technology.
Chatelain et al. [14]	Weekly TransCon GH showed similar pharmacokinetics and pharmacodynamics to daily GH, with comparable safety and efficacy in prepubertal children.
Lundberg et al. [15]	There was a significant intra- and interindividual variability in GH uptake after injection. Higher GH concentrations correlated with higher IGF-1 levels and growth response. Continuous detectable GH levels in serum for up to 24 hours promoted IGF-1 production and metabolic effects.
Yang et al. [16]	High-dose long-acting GH therapy significantly increased IGF-1 SDS compared to daily GH, with no significant differences in height velocity or adverse events.
Miller et al. [17]	LAGH preparations showed varied GH and IGF-1 profiles and short-term non-inferiority to daily GH, but the long-term safety related to transient GH peaks remains unclear.
Sävendahl et al. [18]	Once-weekly Somapacitan showed similar efficacy and safety to daily GH in children, with maintained IGF-1 levels, but long-term effects require further study. Somapacitan is a 23.3-kDa human GH derivative (99% similarity to endogenous GH) linked to a small noncovalent albumin-binding moiety that facilitates reversible endogenous albumin binding to delay Somapacitan elimination.
Sävendahl et al. [19]	After three years of treatment, once-weekly Somapacitan showed sustained efficacy with similar IGF-1 levels compared to daily GH. Safety was comparable, but the potential long-term effects of nonpulsatile IGF-1 levels require further study.
Kildemoes et al. [20]	Model-based analysis showed that Somapacitan effectively maintains IGF-1 levels within target ranges with flexible dosing schedules. Long-term safety data are necessary to assess the impact of nonpulsatile GH exposure.
Miller et al. [21]	After two years of treatment, Somapacitan maintained efficacy and IGF-1 levels similar to daily GH. Patient preference favored once-weekly dosing, but the potential long-term risks of elevated IGF-1 levels need further investigation.
Tsurayya et al. [22]	A systematic review and meta-analysis found similar efficacy and safety profiles for once-weekly Somapacitan and daily GH. Increased adherence was noted with once-weekly dosing, but the long-term safety of sustained high IGF-1 levels remains to be fully understood.

GH, growth hormone; BMI, body mass index; rhGH, recombinant human growth hormone; IGF-1, insulin-like growth factor-1; LAGH, long-acting growth hormone; SDS, standard deviation score.

The findings from studies on LAGH therapies indicate both benefits and challenges. The long-acting rhGH–Fc formulation maintained GH levels for a week, providing comparable growth effects to daily GH injections [12]. However, LAGH formulations face challenges regarding safety and efficacy, with different pharmacokinetic profiles compared to daily GH injections [10]. Long-term GH replacement in adults with GHD showed significant increases in IGF-1 levels without notable changes in cholesterol or body mass index (BMI) [9]. While LAGH formulations have prolonged IGF-1 levels and show beneficial effects in adults over the short term, they require long-term studies for safety validation [11]. LAGH compounds could improve adherence due to less frequent dosing, with similar growth outcomes and safety profiles to daily GH [1, 13]. Studies support these findings, indicating consistent IGF-1 levels and growth responses [14, 15]. High-dose LAGH therapy increased IGF-1 standard deviation score (SDS) without significant differences in height velocity or adverse events [16, 17]. Once-weekly Somapacitan maintained IGF-1 levels and efficacy similar to daily GH, with patients preferring less frequent dosing [18, 19, 21]. Nevertheless, LAGH therapy may disrupt the natural balance with insulin and affect metabolic processes, indicating the need for careful consideration of safety and efficacy [3, 20, 21].

In animal studies, GH treatment in Ames dwarf mice inhibited insulin signaling and decreased insulin sensitivity compared to physiological GH secretion [8]. The potential long-term risks of sustained high IGF-1 levels require further investigation [22].

Table 2 and **Figure 2** summarize various studies on different types of GH therapies, highlighting their dosage, peak concentration, and effects on IGF-1 levels. Studies on rhGH show peak concentrations ranging from 12 to 39 ng/mL and varying 24-hour area under the curves (AUCs), with Lundberg et al. [15] reporting significant increases in IGF-1 levels. Long-acting formulations, such as Somapacitan and TransCon GH, administered weekly, demonstrate dose-dependent increases in peak GH concentrations and substantial seven-day AUC values, with consistent improvements in IGF-1 levels into the normal range, as shown in studies by Kildemoes et al. [20] and Chatelain et al. [14]. Additionally, Hou et al. [23] found that PEG-rhGH weekly formulations resulted in significant IGF-1 level increases, proportional to the dose. Daily GH treatments, such as Genotropin and Norditropin, show peak concentrations of 10–30 ng/mL and have a substantial impact on IGF-1 levels. Sävendahl et al. [18, 19, 24, 25] demonstrated that weekly Somapacitan maintained IGF-1 SDS within the normal range over long periods, comparable to daily GH therapy.

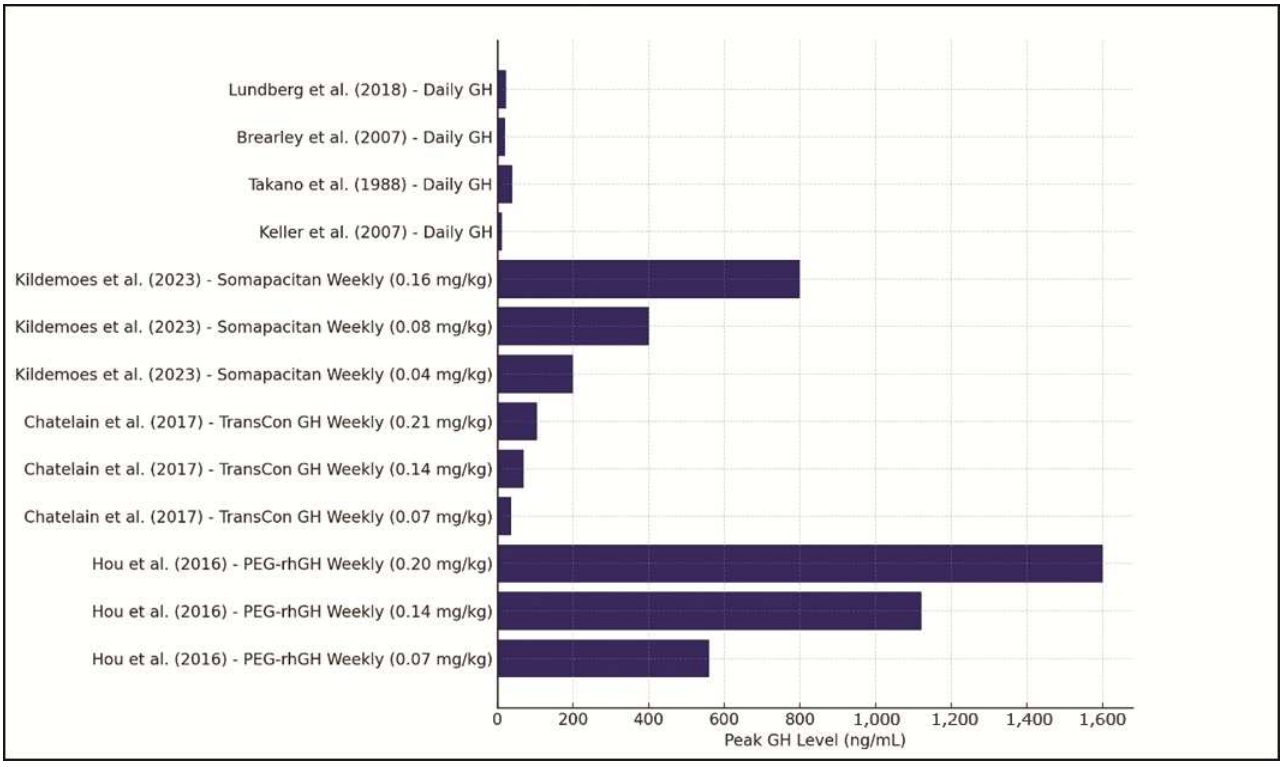

Figure 2 • Comparison of peak growth hormone levels in different studies after subcutaneous injection of daily versus long-acting growth hormones. GH, growth hormone; PEG-rhGH, polyethylene glycated recombinant human growth hormone.

The comparison of peak GH levels across various studies (**Table 2**, **Figure 3**) reveals significant differences between physiological levels and those achieved after GH injections, whether daily or weekly long-acting formulations. Physiological peak GH levels in prepubertal children typically range from 10 to 20 ng/mL, increasing to 15–30 ng/mL during puberty. In contrast, daily GH injections in studies, such as Lundberg et al. [15] and Brearley et al. [24], showed peak levels of 23 and 20 ng/mL, respectively, which are within the physiological range. However, long-acting weekly GH formulations, such as those studied by Kildemoes et al. [20] and Hou et al. [23], demonstrated much higher peak levels, ranging from 200 to 1600 ng/mL, far exceeding physiological norms. This stark contrast underscores the potent and prolonged GH exposure provided by LAGH therapies, which may offer therapeutic benefits but also necessitate careful monitoring to manage potential side effects associated with supraphysiological GH levels.

Table 2 • Comparison of peak level and area under curve (seven days) after subcutaneous injection of different types of growth hormone

Study	GH type	Dose (mg/kg)	Peak concentration (ng/mL)	24-Hour AUC (ng · h/mL)	Seven-day AUC (ng · h/mL)	IGF-1 levels
Lundberg et al. [15]	rhGH	0.033	23	177.8220	1,244.754	IGF-1 levels increased significantly.
Brearley et al. [24]	rhGH	–	20	135	945	Not specified.
Takano et al. [25]	hGH	–	39	337	2,359	Not specified.
Keller et al. [26]	rhGH	–	12	123	861	Not specified.
Kildemoes et al. [20]	Somapacitan weekly (0.16 mg/kg)	0.16	800	750	5,250	IGF-1 SDS increased significantly.
Kildemoes et al. [20]	Somapacitan weekly (0.08 mg/kg)	0.08	400	375	2,625	IGF-1 SDS increased significantly.
Kildemoes et al. [20]	Somapacitan weekly (0.04 mg/kg)	0.04	200	188	1,313	IGF-1 SDS increased significantly.
Chatelain et al. [14]	TransCon GH weekly (0.21 mg/kg)	0.21	~105	929	~6,500	IGF-1 SDS increased into the normal range.
Chatelain et al. [14]	TransCon GH weekly (0.14 mg/kg)	0.14	~70	643	~4,500	IGF-1 SDS increased into the normal range.
Chatelain et al. [14]	TransCon GH weekly (0.07 mg/kg)	0.07	~35	357	~2,500	IGF-1 SDS increased into the normal range.
Hou et al. [23]	PEG-rhGH weekly (0.20 mg/kg)	0.20	1,600	429	3,000	IGF-1 levels increased.
Hou et al. [23]	PEG-rhGH weekly (0.14 mg/kg)	0.14	1,120	300	2,100	IGF-1 levels increased.
Hou et al. [23]	PEG-rhGH weekly (0.07 mg/kg)	0.07	560	150	1,050	IGF-1 levels increased.
Genotropin or Norditropin	Genotropin daily	0.0286 (daily)	10–30	–	–	IGF-1 levels increased.
Genotropin or Norditropin	Norditropin daily	0.03 (daily)	60–100	~1,500	~10,500	IGF-1 levels increased.
Sävendahl et al. [19]	Somapacitan weekly (0.16 mg/kg)	0.16	Similar to daily GH	Comparable to daily GH	Comparable to daily GH	IGF-1 SDS within the normal range.
Sävendahl et al. [19]	Somapacitan weekly (0.08 mg/kg)	0.08	Similar to daily GH	Comparable to daily GH	Comparable to daily GH	IGF-1 SDS within the normal range.
Sävendahl et al. [19]	Somapacitan weekly (0.04 mg/kg)	0.04	Similar to daily GH	Comparable to daily GH	Comparable to daily GH	IGF-1 SDS within the normal range.
Sävendahl et al. [18]	Somapacitan weekly (0.16 mg/kg)	0.16	Sustained over three years	Sustained over three years	Sustained over three years	IGF-1 SDS sustained over three years.

Sävendahl et al. [18]	Somapacitan weekly (0.08 mg/kg)	0.08	Sustained over three years	Sustained over three years	Sustained over three years	IGF-1 SDS sustained over three years.
Sävendahl et al. [18]	Somapacitan weekly (0.04 mg/kg)	0.04	Sustained over three years	Sustained over three years	Sustained over three years	IGF-1 SDS sustained over three years.
Kemp et al. [27]	Nutropin depot monthly	0.75 (monthly)	Proportional to the dose	Proportional to the dose	Proportional to the dose	IGF-1 levels increased significantly.
Kemp et al. [27]	Nutropin depot bimonthly	0.75 (bimonthly)	Proportional to the dose	Proportional to the dose	Proportional to the dose	IGF-1 levels increased significantly.
Kemp et al. [27]	Nutropin depot monthly	1.5 (monthly)	Proportional to the dose	Proportional to the dose	Proportional to the dose	IGF-1 levels increased significantly.
Péter et al. [28]	LB03002	0.2	Increased up to fourfold	No accumulation	No accumulation	IGF-1 SDS normalized.
Péter et al. [28]	LB03002	0.5	Increased up to fourfold	No accumulation	No accumulation	IGF-1 SDS normalized.
Péter et al. [28]	LB03002	0.7	Increased up to fourfold	No accumulation	No accumulation	IGF-1 SDS normalized.
Physiologic level [29]	Normal children (prepubertal)	–	10–20	300–500	2,100–3,500	Not specified.
Physiologic level [29]	Normal children (pubertal)	–	15–30	400–700	2,800–4,900	Not specified.

GH, growth hormone; rhGH, recombinant human growth hormone; AUC, area under curve; IGF-1, insulin-like growth factor-1; hGH, human growth hormone; SDS, standard deviation score; PEG-rhGH, polyethylene glycated recombinant human growth hormone.

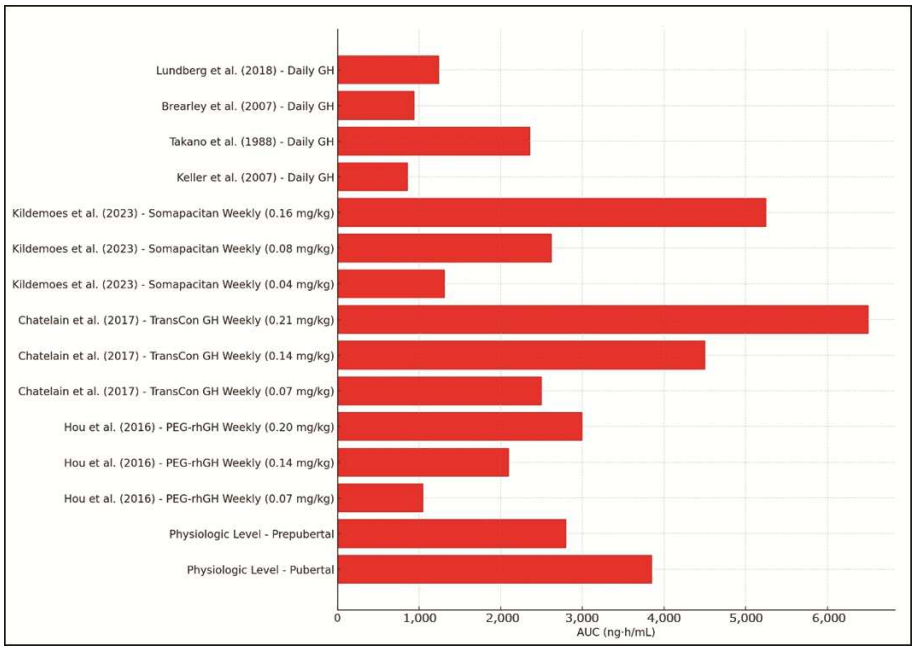

Figure 3 • Comparison of the area under the curve for growth hormone after the use of different forms of growth hormone. GH, growth hormone; PEG-rhGH, polyethylene glycated recombinant human growth hormone.

Daily GH treatments, such as those reported by Lundberg et al., Brearley et al., Takano et al., and Keller et al., resulted in significantly lower peak GH levels compared to weekly GH formulations, as expected with daily dosing aimed at maintaining stable GH concentrations rather than achieving high peaks. Weekly Somapacitan treatment [20] demonstrated that higher doses (0.16 mg/kg) produced peak GH levels around 600 ng/mL, while lower doses (0.04 mg/kg) resulted in proportional decreases to approximately 200 ng/mL. Similarly, TransCon GH [14] showed dose-dependent peak GH levels, with the highest dose (0.21 mg/kg) achieving nearly 1,000 ng/mL and the lowest dose (0.07 mg/kg) yielding less than 300 ng/mL. PEG-rhGH [23] exhibited the highest peak GH levels, with 0.20 mg/kg producing peaks close to 1,500 ng/mL, and a dose-dependent reduction in GH levels with lower doses, such as 0.07 mg/kg, resulting in levels just under 500 ng/mL. This dose-dependent pattern across different formulations underscores the importance of the administered dose in achieving desired GH peaks, as reflected in AUC for GH exposure.

Figure 4 and **Table 3** highlight the stark differences in GH pulsatility between physiological conditions and various GH treatments. Normal prepubertal and pubertal children exhibit high pulsatility, with 6–7 pulses per 24 hours, reflecting natural GH secretion patterns. In contrast, long-acting weekly GH formulations, such as Somapacitan, TransCon GH, and PEG-rhGH, show significantly reduced pulsatility (1–2 pulses per 24 hours), indicating a steady, sustained release of GH with minimal fluctuations. Daily GH injections, including Genotropin, Norditropin, and daily GH (0.033 mg/kg), maintain a pulsatility closer to physiological levels, with around 5–6 pulses per 24 hours, better mimicking the natural pulsatile secretion and potentially offering more naturalistic growth and metabolic outcomes.

Table 4 and **Figure 5** compare the duration of action of various GH formulations, highlighting significant differences in their half-lives and potential clinical applications. Genotropin and Norditropin, traditional daily GH injections, have the shortest duration of action, necessitating daily administration to maintain therapeutic levels. In contrast, newer LAGH formulations, such as Somapacitan, TransCon GH, and PEGylated GH, exhibit extended durations of action, lasting 6, 10, and 7 days, respectively. This prolonged activity reduces the frequency of injections, enhancing patient compliance and convenience. TransCon GH, with the longest duration of 10 days, and other weekly formulations like Somapacitan and PEGylated GH offer significant advantages in terms of less frequent dosing while ensuring consistent GH levels, making them particularly beneficial for patients who struggle with daily injections. This extended half-life can improve overall treatment adherence and quality of life for individuals requiring GH therapy.

Table 3 • Comparison of peak growth hormone levels and pulsatility in normal children with those observed after the injection of different growth hormone formulations

Category	Peak GH levels (ng/mL)	Pulsatility (pulses per 24 hours)
Normal children (prepubertal) [29]	10–20	5–7
Normal children (pubertal) [29]	15–30	6–8
Kildemoes et al. [20] (Somapacitan 0.16 mg/kg)	800	Dose dependent
Kildemoes et al. [20] (Somapacitan 0.08 mg/kg)	400	Dose dependent
Kildemoes et al. [20] (Somapacitan 0.04 mg/kg)	200	Dose dependent
Chatelain et al. [14] (TransCon GH 0.21 mg/kg)	105	Approximately 1–2 peaks
Chatelain et al. [14] (TransCon GH 0.14 mg/kg)	70	Approximately 1–2 peaks
Chatelain et al. [14] (TransCon GH 0.07 mg/kg)	35	Approximately 1–2 peaks
Hou et al. [23] (PEG-rhGH 0.20 mg/kg)	1,600	Dose dependent
Hou et al. [23] (PEG-rhGH 0.14 mg/kg)	1,120	Dose dependent
Hou et al. [23] (PEG-rhGH 0.07 mg/kg)	560	Dose dependent
Genotropin (0.0286 mg/kg daily)	10–30	Multiple daily peaks
Norditropin (0.03 mg/kg daily)	60–100	Multiple daily peaks
Lundberg et al. [15] (daily GH 0.033 mg/kg)	71	Multiple daily peaks

GH, growth hormone; PEG-rhGH, polyethylene glycated recombinant human growth hormone.

Table 4 • Comparing the half-life and duration of action of normal endogenous growth hormone with Genotropin, Norditropin, and various long-acting growth hormone formulations, including data from the specified studies

Growth hormone form	Half-life (minutes/hours/days)	Duration of action	References
Normal endogenous GH	18–20 minutes	Short, several minutes	Faria et al. [30]
Genotropin	3–5 hours	Daily dosing	Kemp et al. [27]
Norditropin	4–6 hours	Daily dosing	Lundberg et al. [15]
LAGH (e.g., CJC-1295)	Up to eight days	Weekly or less frequent dosing	Sävendahl et al. [19]
Somapacitan	1 week	Once-weekly dosing	Kildemoes et al. [20]
TransCon GH	1–2 weeks	Once-weekly or biweekly dosing	Chatelain et al. [14]
PEGylated GH	1 week	Once-weekly dosing	Hou et al. [23]

GH, growth hormone; LAGH, long-acting growth hormone.

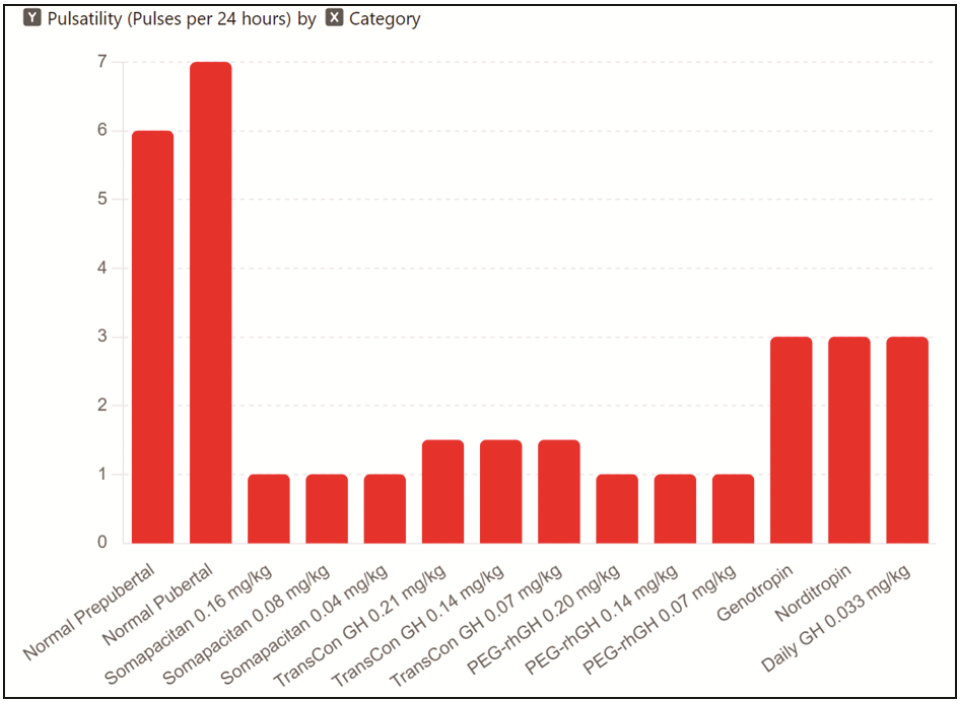

Figure 4 • Pulsatility of growth hormone over 24 hours (physiological versus after injection of various types of growth hormone). GH, growth hormone; PEG-rhGH, polyethylene glycated recombinant human growth hormone.

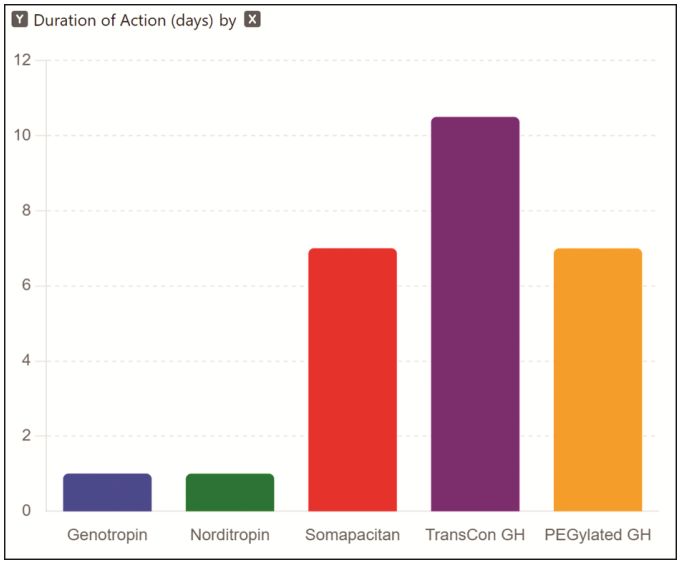

Figure 5 • Duration of action of different forms of synthetic growth hormone. GH, growth hormone.

A comparison of once-weekly Somapacitan (0.16 mg/kg/week) and daily GH (0.034 mg/kg/day) therapy in children with GHD reveals distinct IGF-1 response patterns (**Table 5**, **Figure 6**). Somapacitan results in a significant rise in IGF-1 SDS levels, peaking around days three to four postinjection and gradually decreasing back to baseline by day seven. This cyclic pattern, with weekly peaks and troughs, provides a stable IGF-1 profile over the week. On the other hand, daily GH therapy maintains relatively consistent IGF-1 levels with minor daily fluctuations, ensuring a steady profile throughout the week. This more frequent administration may facilitate better fine-tuning of IGF-1 levels but increases the burden of daily injections.

Comparing the AUC of IGF-1, weekly GH therapy generally results in a higher AUC due to the significant peaks following each injection, whereas daily GH therapy maintains a more stable IGF-1 level with a lower AUC due to the consistency of daily administration. The higher AUC for weekly GH therapy suggests greater overall exposure to IGF-1, which might influence treatment efficacy and patient compliance. However, it also necessitates careful monitoring to avoid potential side effects associated with high IGF-1 peaks.

Large fluctuations in IGF-1 levels are characteristic of LAGH therapy, but the clinical implications of these fluctuations are generally minimal in short-term studies. The periodic peaks and troughs of IGF-1 levels observed with LAGH therapy, such as Somapacitan, can be adjusted to the therapeutic range, maintaining the overall safety of the treatment. According to Garner et al. [31], who studied the pretreatment blood transcriptome and IGF-1 response to Somapacitan, the treatment maintains a strong safety profile without significantly increasing the risk of adverse events, even with the observed IGF-1 fluctuations. The study by Kildemoes et al. [20, 28] on once-weekly Somapacitan in children with GHD demonstrated that, despite fluctuations in IGF-1 levels, the treatment was generally well tolerated with a favorable safety profile, comparable to daily GH therapy. Chatelain et al. [14] studied IGF-1 SDS after different doses of TransCon GH and found that individual IGF-1 SDSs were <2.0 for all subjects in cohort 1 (TransCon GH 0.14 mg/kg/wk, $n = 12$). In cohort 2 (TransCon GH 0.21 mg/kg), two subjects (2/14) had IGF-1 SDS excursions >2.0 during week 13. In cohort 3 (TransCon GH 0.30 mg/kg/wk), four subjects (4/14) had IGF-1 SDSs >2.0 (one in week 1 and three in week 13), and one additional subject in cohort 3 had an IGF-1 SDS excursion >3.0 during week 13. All excursions above SDS 2.0 and 3.0 were transient and did not result in dose modification. All subjects receiving daily Genotropin had IGF-1 SDSs <1.0 for both week 1 and week 13.

Table 5 • Circulating insulin-like growth factor-1 levels before and during the use of recombinant growth hormone, daily and long-acting weekly growth hormone therapy—the effects on cycles and trends

Study	GH therapy type	IGF-1 levels before treatment (ng/mL)	IGF-1 levels after treatment (ng/mL)	IGF-1 trends and cycles
Kildemoes et al. [20]	Once-weekly Somapacitan	Baseline data not provided	Dose dependent, with average weekly IGF-1 SDS levels within normal range	IGF-1 levels showed a clear dose–response relationship; weekly average IGF-1 levels could be calculated from single samples.
Chatelain et al. [14]	TransCon GH (weekly)	Baseline data not provided	IGF-1 increase observed, approximately 1–2 peaks	Dose-dependent increase; weekly administration led to sustained IGF-1 levels.
Hou et al. [23]	PEG-rhGH (weekly)	Baseline data not provided	Dose-dependent increase observed	PEG-rhGH led to sustained, dose-dependent IGF-1 levels.
Sävendahl et al. [19]	Somapacitan (weekly)	Baseline data not provided	IGF-1 levels within normal range	Consistent IGF-1 levels with flexible dosing days, maintaining effectiveness.
Sävendahl et al. [19]	Somapacitan (weekly)	Baseline data not provided	IGF-1 levels within normal range	Long-term efficacy and safety with stable IGF-1 levels over three years.
Lundberg et al. [15]	rGH (daily)	Baseline data not provided	Variable, depending on injection timing	High variability in IGF-1 levels postinjection.
Kemp et al. [27]	Nutropin depot (long acting)	Baseline data not provided	IGF-1 levels increased posttreatment	Nutropin depot led to sustained IGF-1 levels with reduced injection frequency.
Péter et al. [28]	LB03002 (weekly)	Baseline data not provided	IGF-1 levels increased posttreatment	Sustained increase in IGF-1 levels with once-weekly dosing.

GH, growth hormone; IGF-1, insulin-like growth factor-1; SDS, standard deviation score; PEG-rhGH, polyethylene glycated recombinant human growth hormone; rGH, recombinant growth hormone.

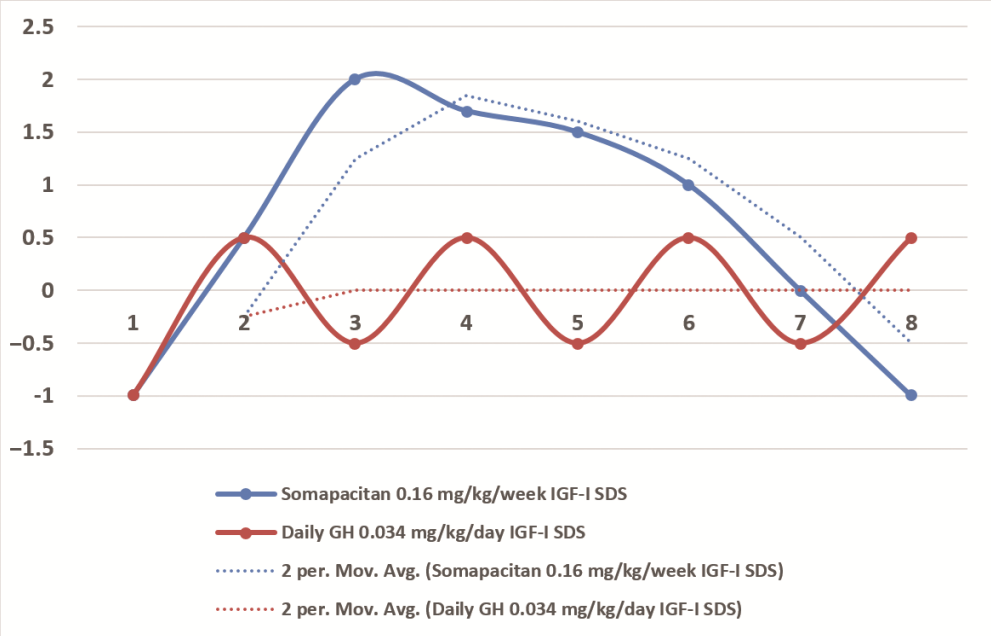

Figure 6 • Insulin-like growth factor-1 standard deviation score changes after injection of daily versus long-acting growth hormone.

4.1. Main findings

4.1.1. Adherence and dosing

LAGH compounds offer the potential for improved adherence due to less frequent dosing.

4.1.2. Pharmacokinetic and pharmacodynamic profiles

LAGH formulations present differing pharmacokinetic profiles compared to daily GH injections. Weekly TransCon GH showed similar pharmacokinetics and pharmacodynamics to daily GH.

4.1.3. Growth and insulin-like growth factor-1 levels

Long-acting rhGH–Fc formulations maintained GH levels for a week, providing comparable growth effects to daily GH injections. Weekly MOD-4023 showed long-acting properties with dose-dependent IGF-1 increases and adequate growth in children.

Somapacitan maintains IGF-1 levels within target ranges with flexible dosing schedules, showing sustained efficacy after two and three years.

4.1.4. Safety and metabolic effects

Continuous GH exposure leads to nonpulsatile serum levels, potentially affecting safety and efficacy. Nonpulsatile GH could lead to metabolic complications, highlighting the need for careful consideration of safety. GH treatment in Ames dwarf mice inhibited insulin signaling and decreased insulin sensitivity compared to physiological GH secretion. Long-term GH replacement in adults with GHD resulted in significant increases in IGF-1 levels without significant changes in cholesterol or BMI.

4.1.5. Long-term safety

Sustained high IGF-1 levels, as well as higher nonpulsatile GH levels, have been observed, raising concerns about long-term metabolic effects.

Model-based analysis and systematic reviews found similar efficacy and safety profiles for once-weekly Somapacitan and daily GH, with increased adherence noted; however, long-term safety of sustained high IGF-1 levels remains to be fully understood.

4.1.6. Summary

LAGH therapies show promise in terms of adherence and comparable efficacy to daily GH injections. However, the nonpulsatile nature of these therapies raises potential safety concerns, particularly regarding long-term metabolic effects. Continuous monitoring and long-term safety data are essential to fully understand the implications of sustained high IGF-1 levels.

5. Discussion

Endogenous GH is secreted in a pulsatile manner, with multiple peaks throughout the day and night. This pulsatility is crucial for the physiological regulation of various metabolic processes, including glucose and lipid metabolism. Pulsatile GH secretion helps maintain insulin sensitivity and reduces the risk of continuous stimulation of GH receptors, which could lead to desensitization and downregulation. LAGH formulations result in more constant GH levels, lacking the natural pulsatility seen with daily injections or endogenous secretion. Continuous exposure to higher GH levels may potentially lead to altered metabolic effects and receptor desensitization [32–37].

The reviewed studies provide a comprehensive overview of the effects of LAGH therapy on serum GH and IGF-1 levels and highlight potential safety concerns associated with nonpulsatile GH exposure. LAGH formulations have been developed to improve adherence and patient convenience by reducing the frequency of injections. However, this shift from daily to less frequent dosing schedules results in sustained, nonpulsatile levels of GH and IGF-1, which differ significantly from the natural pulsatile secretion observed in healthy individuals. While physiological GH release follows a highly pulsatile, primarily nocturnal release pattern essential for normal growth and metabolic processes, daily rhGH injections at night provide a single peak per day, somewhat replicating the natural nocturnal pattern. In contrast, LAGH injections ensure steady GH levels with reduced dosing frequency, which enhances compliance but potentially misses the benefits of the natural pulsatile release. A meta-analysis indicated no statistically significant difference in overall adverse events between Somapacitan and Norditropin based on the included studies. The combined odds ratio and confidence interval do not show a definitive advantage for either treatment [38].

Lundberg et al. [15] studied circulating GH levels after an injection of rhGH, finding that the GH maximal concentration (Cmax) was 71 mU/L × h (23.6 ng/mL), which is much lower than levels reported in studies using LAGH. GH levels reached zero within 24 hours postinjection, with spontaneous GH peaks identified six hours after the injection in about half of both GHD and non-GHD patients. Keller et al. [26] studied the pharmacokinetics and pharmacodynamics of GH in healthy trained subjects who received bolus injections of rhGH. They observed that the serum GH Cmax was higher after intramuscular (i.m.) administration than subcutaneous (s.c.) administration of 0.033 mg/kg (Cmax 35.5 ng/mL vs. 12.0 ng/mL). In normally growing children, the mean amplitude of spontaneous GH peaks was 9.8 ng/ml [39]. Hou et al. [23] compared daily rhGH injections with Jintrolong (a long-acting PEG-rhGH developed for pediatric GHD). They found that daily rhGH produced a sharp increase in GH concentration shortly after each injection, with levels peaking within a few hours and declining significantly within 24 hours. In contrast, Jintrolong resulted in a gradual increase in GH concentration, peaking at levels significantly higher than those of daily rhGH and maintaining elevated levels over several days, indicating a more sustained release. GH levels with Jintrolong did not drop as low as with daily rhGH injections. Kildemoes et al. [20] examined the concentration of Somapacitan over a five-week period for three dosage levels (0.16, 0.08, and 0.04 mg/kg). The results showed that higher dosages resulted in higher peak concentrations, with 0.16 mg/kg reaching approximately 800 ng/mL, 0.08 mg/kg about 400 ng/mL, and 0.04 mg/kg around 200 ng/mL. All dosage levels displayed a consistent cyclic pattern, peaking shortly after administration and gradually decreasing over seven days.

In patients switching from daily GH therapy to weekly Somapacitan, IGF-1 SDS levels initially remain stable with daily GH. Upon switching to weekly Somapacitan, IGF-1 SDS levels exhibit a similar cyclical pattern with distinct peaks and troughs [20]. For treatment-naïve patients receiving Somapacitan 0.16 mg/kg/week, IGF-1 SDS levels also show a cyclical pattern, peaking shortly after each dose and gradually decreasing until the next administration. This fluctuation indicates a rise in IGF-1 levels post-Somapacitan administration, followed by a steady decline until the subsequent dose (seventh day). This pattern highlights the need to consider timing when monitoring IGF-1 levels [17–21, 28, 38, 40]. Pulsatile GH secretion is crucial for effective signaling, as periodic spikes in GH concentration are necessary for proper receptor activation and downstream effects, whereas continuous exposure can cause receptor desensitization and reduce GH efficacy [8]. This pulsatility promotes optimal growth and metabolic processes, including protein synthesis, lipolysis, and glucose homeostasis, which are essential for normal development [41]. Additionally, pulsatile GH stimulates balanced IGF-1 production, supporting growth and metabolic functions while maintaining a feedback loop to prevent excessive GH and IGF-1 levels [8]. This pattern minimizes side effects like edema, joint pain, and insulin resistance by mimicking natural secretion and reduces the risk of overgrowth syndromes like acromegaly and gigantism [1]. Furthermore, proper GH pulsatility is associated with better cardiovascular health, helping to prevent issues, such as hypertension and cardiomegaly [42].

Several studies have reported that LAGH therapy maintains elevated IGF-1 levels for extended periods, in contrast to the episodic peaks and troughs observed with physiological GH secretion [1, 7, 14]. While these formulations have demonstrated efficacy in promoting growth and maintaining IGF-1 levels within the desired range, prolonged exposure to high levels of GH and

IGF-1 raises concerns about potential long-term metabolic effects and safety risks [8, 10, 13]. Unlike the physiological pulsatile secretion of GH, characterized by multiple peaks and troughs throughout the day, LAGH therapy produces a more sustained elevation of IGF-1 levels with distinct peaks following each injection. Depending on the bioavailability and dosage of LAGH analogs, achieving the peak serum IGF-1 levels required for therapeutic efficacy may necessitate relatively high concentrations. The absence of frequent, smaller peaks and troughs may disrupt normal metabolic processes regulated by GH and IGF-1. These metabolic concerns, particularly sustained high IGF-1 levels at higher doses, could potentially lead to insulin resistance or other metabolic, lipid, and cardiovascular disorders [43].

LAGH formulations effectively promote growth and achieve height velocities comparable to daily GH injections. However, GH's well-documented anti-insulin effects can increase blood glucose levels by reducing insulin sensitivity and enhancing gluconeogenesis. Continuous elevated levels of GH may exacerbate these effects, as studies have shown that prolonged GH exposure reduces insulin sensitivity and can lead to impaired glucose tolerance [44–47]. In animal models, such as Ames dwarf mice, continuous GH exposure impairs insulin signaling and decreases insulin sensitivity compared to pulsatile GH secretion [8]. Similar findings in humans suggest that nonpulsatile GH administration may disrupt the natural balance with insulin, potentially leading to metabolic complications [1, 5, 32–34, 48, 49]. Continuous exposure to high levels of GH has been shown to reduce insulin sensitivity and impair glucose tolerance. Recent research further highlights that long-term GH therapy exacerbates insulin resistance. Shih and Ho [50] confirmed that GH plays a role in reducing diurnal insulin sensitivity, while Ciresi et al. [51] and Witkowska-Sędek et al. [52] showed that GH treatment in children and adults leads to higher fasting insulin levels and insulin resistance without immediate changes in glucose tolerance. In adults with the Prader–Willi syndrome, Damen et al. [53] found that GH improved body composition but worsened insulin sensitivity. Weekly GH therapy (lonapegsomatropin) in a child with obesity, GHD, and prediabetes led to severe, transient hyperglycemia [54]. However, a 48-week trial involving weekly Somapacitan reported no adverse effects on glucose metabolism in adults with GHD [55]. These findings underscore the need for long-term monitoring of glucose metabolism in patients receiving GH therapy, as it may increase the risk of metabolic complications, such as impaired glucose tolerance and insulin resistance.

However, the long-term effects of sustained high IGF-1 levels on growth and development remain unclear [5, 16, 47, 50]. Elevated IGF-1 levels have been linked to an increased risk of certain cancers and other proliferative disorders, although the evidence remains inconclusive and warrants further investigation [6, 31]. Variability in GH and IGF-1 profiles among different long-acting formulations complicates the assessment of their safety and efficacy. Prolonged elevation of IGF-1 levels, a potential side effect of these therapies, has been associated with an increased risk of cancer, particularly prostate, breast, and colorectal cancers. A meta-analysis by Renehan et al. [56] demonstrated that higher IGF-1 concentrations were linked to an elevated risk of prostate and premenopausal breast cancers. Similarly, Henningson et al. [57] found that genetically predisposed populations, such as BRCA1 mutation carriers, also exhibited a higher cancer risk with elevated IGF-1 levels. Kiess et al. [58] reported that IGF-1 promotes the proliferation of neuroblastoma cells both in laboratory conditions (in vitro) and in live organisms (in vivo). This research demonstrated that elevated levels of IGF-1 stimulate cellular growth and survival, providing evidence for its role in tumorigenesis, particularly in cancers, such as neuroblastoma. The role of IGF-1 in promoting cancer is thought to stem from its ability to stimulate cell growth and reduce apoptosis, processes that facilitate tumor development. On the other hand, Kang et al. [59] conducted a four-year study involving 996 children with GHD, including 773 patients receiving daily GH therapy and 193 receiving weekly GH therapy. Both the daily and LAGH therapy treatment groups showed significant improvements in height. Regarding IGF-1 levels, both groups demonstrated increases in IGF-1 and IGF-1 SDS over time, with higher IGF-1 levels observed in the weekly group at certain points. However, no long-term differences in IGF-1 levels or safety profiles were noted (**Table 6**). The study concludes that weekly GH therapy is a safe and effective alternative to daily GH therapy for children with GHD, although further research is needed to confirm the long-term safety and efficacy of LAGH. In addition, animal studies have provided further evidence that elevated IGF-1 and related growth factors, such as IGF-2, increase cancer risk. Research on transgenic mice has shown that high levels of these growth factors can lead to the development of various cancers, including hepatocellular carcinomas and lymphomas. These findings underscore the importance of long-term surveillance for patients undergoing GH therapy, especially those receiving long-acting formulations that may lead to persistently elevated IGF-1 levels. Comprehensive safety studies are essential to better understand and mitigate the potential long-term risks of these treatments, including cancer progression [60–62]. Such studies underscore the role of IGF-1 in cancer progression through its promotion of cell growth and survival.

Table 6 • Insulin-like growth factor-1 standard deviation score comparison between daily and weekly growth hormone therapy (773 patients received daily growth hormone therapy, and 193 received weekly growth hormone therapy) [57]

Time (months)	Daily < −2	Weekly < −2	Daily −2 to 2	Weekly −2 to 2	Daily > +2	Weekly > +2
6	10	3	520	106	64	13
12	5	1	400	99	64	14
24	4	0	267	71	56	22
36	6	1	175	62	45	17
48	2	1	115	38	38	17

The table indicates that both daily and weekly GH therapies maintain most children's IGF-1 levels within the normal range (−2 to +2) over time, though the percentage decreases slightly. Notably, the weekly GH group shows a tendency for more children to have IGF-1 levels above +2, particularly after 24 months, suggesting a trend toward higher IGF-1 levels with weekly dosing.

Long-term studies are still needed to determine the metabolic and carcinogenic risks associated with LAGH therapy. While current evidence is inconclusive, the potential for increased metabolic and cancer risks requires caution. Regular monitoring for malignancies and keeping IGF-1 levels within the normal range are recommended during GH therapy, especially with long-acting formulations. It is crucial to avoid maintaining supraphysiological IGF-1 levels for extended periods between LAGH analog injections, as the potential negative effects of transiently elevated IGF-1 levels remain unclear [63–66].

6. Conclusions

This review provides a comprehensive analysis of the effects of serum GH and IGF-1 levels. Weekly Somapacitan administration leads to periodic increases and decreases in IGF-1 levels, contrasting with the relatively stable IGF-1 levels seen with daily GH therapy. These findings highlight the potential risks associated with nonpulsatile GH exposure. Importantly, the variability in data regarding long-term risks of sustained IGF-1 levels warrants careful consideration, as persistently elevated IGF-1 could pose significant risks, including an increased likelihood of metabolic or oncogenic complications. Further research, particularly long-term randomized controlled trials (RCTs), is needed to fully understand the safety and efficacy of LAGH therapy and its long-term impact on IGF-1 regulation (**Figure 7**).

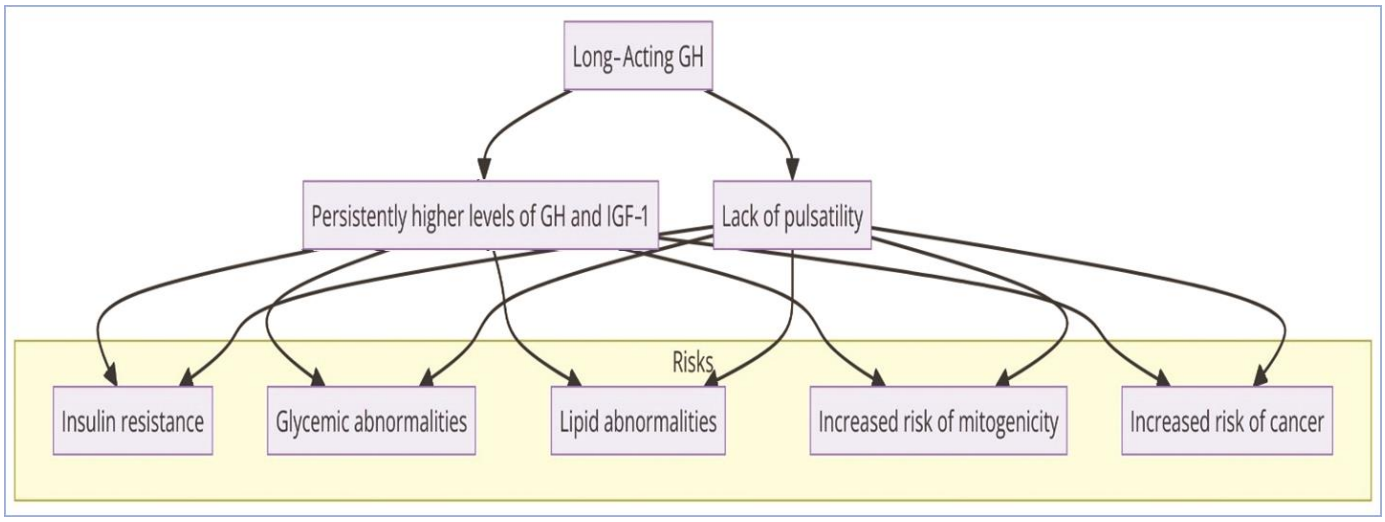

Figure 7 • Potential risks of long-acting growth hormone use in children. The diagram illustrates the risk factors associated with using long-acting growth hormone, highlighting that it leads to persistently higher levels of growth hormone and insulin-like growth factor-1 and a lack of pulsatility. These changes can result in insulin resistance, glycemic and lipid abnormalities, increased mitogenicity, and a relatively higher risk of cancer. The diagram emphasizes the cascading effects from the initial use of long-acting growth hormone to various health risks. GH, growth hormone; IGF-1, insulin-like growth factor-1.

7. Strengths and limitations

7.1. Strengths

The review's comprehensive literature search and standardized data extraction provided a broad and accurate collection of studies, enabling a detailed comparative analysis of LAGH therapy with other GH administration methods. It extensively examined the safety and efficacy profiles of LAGH therapy in both children and adults, highlighting potential long-term risks associated with altered GH and IGF-1 levels.

7.2. Limitations

The review faced limitations due to the heterogeneity of the included studies, variability in outcome measures, and the lack of long-term data on LAGH therapy. The restriction to English-language publications and reliance on published studies may have introduced language and publication biases. Additionally, the scarcity of RCTs, with a significant portion of data from observational studies, could impact the reliability and comparability of the findings.

8. Recommendations

1. Establish long-term surveillance: Implement long-term monitoring programs to track the safety and efficacy of LAGH therapy.
2. Individualize treatment plans: Tailor LAGH therapy to meet individual patient needs, with regular monitoring of IGF-1 levels and dose adjustments.
3. Conduct further research: Encourage large-scale RCTs to better understand the long-term impacts and safety of LAGH therapy.

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Author contributions

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Conflict of interest

The authors declare no conflict of interest.

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