EXPERT REVIEWS

Adult growth hormone deficiency: clinical advances and approaches to improve adherence

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Short title: Advances and adherence in adult growth hormone deficiency.

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Abstract

Introduction: There has been significant clinical advances in the understanding of the diagnosis and benefits of long-term recombinant human growth hormone (rhGH) replacement in adults with GH deficiency (GHD) since its approval in 1996 by the United States Food and Drug Administration.

Areas covered: We searched PubMed, Medline, CINAHL, EMBASE and PsychInfo databases between January 2000 and June 2019 for published studies evaluating adults with GHD. We reviewed the data of the oral macimorelin test compared to the GHRH plus arginine and the insulin tolerance tests that led to its approval by the United States FDA and European Medicines Agency for adult diagnostic testing. We summarize the clinical advances of long-term benefits of rhGH therapy and the potential effects of GH receptor polymorphisms on individual treatment responsiveness. We identify that non-adherence and discontinuation rates are high and recommend strategies to support patients to improve adherence. We also provide an overview of several long-acting GH (LAGH) preparations currently under development and their potential role in improving treatment adherence.

Expert commentary: This article summarizes recent clinical advances in rhGH replacement therapy, the biological and molecular aspects that may influence rhGH action, and offers practical strategies to enhance adherence in adults with GHD.

1. Introduction

Adult growth hormone deficiency (GHD) is a well-defined clinical entity characterized by abnormal body composition, unfavorable cardiovascular risk, cardiac dysfunction, decreased bone mineral density (BMD), glucose intolerance, and impaired quality of life (QoL) [1, 2]. Recent studies have suggested increased mortality in patients with hypopituitarism [3-7], particularly in women and in patients diagnosed at a younger age [5, 6]. Growth hormone deficiency has been implicated, although other factors such as under- [3] or over-treatment [4] with glucocorticoid replacement therapy for secondary adrenal insufficiency and underlying etiology of the hypothalamic-pituitary disease (e.g., craniopharyngioma and/or previous history of multiple surgeries and cranial irradiation) are also important contributing factors [8, 9]. Whether long-term recombinant human GH (rhGH) therapy normalizes or decreases mortality rates in patients with hypopituitarism remains unresolved.

Adult GHD may present as childhood-onset (CO-GHD) or adult-onset (AO-GHD) GHD. The most frequent cause of CO-GHD is idiopathic and may be the only pituitary hormone deficiency. Other causes of CO-GHD include congenital causes (e.g., genetic abnormalities), structural defects (e.g., pituitary formation abnormalities, optic nerve hypoplasia, hydrocephalus, arachnoid cyst, midline facial defects such as single central incisor, cleft lip, and cleft palate), and acquired causes (e.g., perinatal insults, intracranial tumors such as germinomas, cranial irrradiation for intracranial tumors, and pituitary tumors). By contrast, AO-GHD is frequently acquired with hypothalamic-pituitary tumors and/or their treatment with surgery and cranial irradiation being the main causes [10, 11]. Current recommended regimens of rhGH replacement therapy are effective in

restoring linear growth and improving adult height outcomes of children with GHD [12], whereas in adults, the primary objective of rhGH replacement is to improve metabolic and psychological abnormalities [13-16].

We reviewed studies published between January 2000 and June 2019 in PubMed, Medline, CINAHL, EMBASE and PsychInfo databases. The search was performed using the terms "adult" and "replacement therapy" as subheadings of the term "growth hormone deficiency" in the Medical Subject Headings (MeSH) thesaurus. The selection included prospective and retrospective studies, and clinical reviews on diagnosis, benefits, side-effects, adherence and treatment outcomes of rhGH replacement therapy in adults with GHD. We also summarize our current knowledge of the macimorelin test as the approved diagnostic test for adult GHD by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and discuss the potential effects of GH receptor polymorphisms on individual treatment responsiveness. Finally, we offer practical strategies to improve adherence to rhGH therapy, and provide a brief overview of long-acting GH (LAGH) preparations under development.

2. Clinical advances in the management of adult GHD

2.1 Diagnosis of adult GHD

Diagnosis of adult GHD is often challenging due to lack of a single biological end-point, unlike growth failure in children with the disorder. As serum GH and IGF-I levels decline with aging, it is important to differentiate between age-related physiological decrease in GH levels and pathological GHD that usually has an identifiable etiology. Additionally, GH is secreted episodically in a pulsatile pattern modified by age, gender, and BMI;

whereas serum IGF-I levels can be lowered by factors such as malnutrition, chronic hyperglycemia, illness, renal failure, and liver disease [17]. In the majority of patients, GH stimulation test/s are required to establish the diagnosis, with the exception of patients with hypothalamic-pituitary disease who have at least 3 other pituitary hormone deficiencies and low serum IGF-I levels [< -2.0 standard deviation score (SDS)] [18], patients with genetic defects affecting the hypothalamic-pituitary axes, and those with hypothalamic-pituitary structural brain defects [11]. In children with idiopathic GHD, retesting during transition to adult care services after at least 1 month following discontinuation of rhGH therapy, is recommended [11, 19, 20]. Several sub-populations of patients (e.g., traumatic brain injury, subarachnoid hemorrhage, ischemic stroke, infections in the central nervous system, congenital hydrocephalus, and snake bite) have been identified in recent years to be at risk for developing hypopituitarism, including adult GHD [21, 22]. However, the diagnostic accuracy and reliability of currently available GH stimulation tests in some of these newly described sub-populations have not been adequately studied.

The insulin tolerance test (ITT) has historically been accepted as the gold standard GH stimulation test, but is used less frequently today in the United States because it is labor-intensive, unpleasant for some patients, and contraindicated in the elderly and in those at risk of seizure disorders and cardio/cerebrovascular disease [23]. When recombinant GHRH (Geref®) was removed from the United States market in July 2008, it was debated as to which test should be used in place of the GHRH plus arginine test as the alternative to the ITT [24]. The arginine test is not a reliable alternative as its diagnostic accuracy is poor and requires a very low peak GH cut-point of 0.4 μg/L [25].

The glucagon stimulation test (GST) was proposed in 2009 as the alternative to the ITT [24], based on the available data at that time [26-28], and has since become the most commonly used diagnostic test for adult GHD in the United States because of its availability, reproducibility, safety, lack of influence by gender and hypothalamic cause of GHD, and relatively few contraindications [23]. The accuracy of GST is acceptable in normal weight individuals, but because peak GH secretion decreases with increasing body mass index (BMI) [29], a lower peak GH cut-point of 1 μg/L has been suggested in overweight/obese patients [30]. The major drawbacks of the GST are the long test duration (3 to 4 hours), the need for intramuscular administration, and the relatively frequent incidence of nausea and vomiting [31].

In December 2017 and January 2019, the FDA and EMA approved macimorelin for use as a diagnostic test for adult GHD in the United States [32] and Europe [33], respectively. Macimorelin is an orally active ghrelin-mimetic that binds to the GHS-R1a receptor with similar affinity to ghrelin. It is a pseudo-tripeptide with increased stability and oral bioavailability compared with other GH secretagogues, such as GHRP-6. The drug is well absorbed in the gastrointestinal tract and effectively stimulates endogenous GH secretion in healthy volunteers with good tolerability [34]. An open-label, crossover, multicenter study tested the diagnostic accuracy of macimorelin (0.5 mg/kg) compared to the GHRH plus arginine test in adults with GHD and healthy matched controls [35]. Peak GH levels were 2.36 ± 5.69 and 17.71 ± 19.11 μg/L in adults with GHD and healthy controls, respectively, with GH cut-points ranging between 2.7 and 5.2 μg/L [35] showing good discrimination comparable to GHRH plus arginine. Macimorelin was subsequently compared to the ITT in a multicenter, open-label, randomized, 2-way

crossover study [36], and was found to be a simple, highly reproducible, and safe test, with optimal GH cut-points ranging from 4.6 to 8.1 μg/L. To minimize the potential of misclassifying some patients, the FDA selected the GH cut-point of 2.8 μg/L, the low end of the range suggested by the previously published data [35], to make the diagnosis of adult GHD. Interestingly, if the GH cut-point was increased to 5.1 μg/L, the identical cut-point to the ITT [11, 20], optimal negative and positive agreements (94% and 82%, respectively) with 92% sensitivity and 96% specificity was observed. In fact, this higher GH cut-point increased the sensitivity of the test while maintaining the specificity of the 2.8 μg/L cut-point with good overall agreement with the ITT. Advantages of macimorelin include its oral administration, short test duration lasting 90 minutes, only 3 to 4 blood sample collections required, and no reported hypoglycemia. The test was well-tolerated and mild dysgeusia was the most common side-effect, which resolved spontaneously [36]. Because macimorelin may interact with other drugs potentially inducing QT prolongation, such as antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, or reduce plasma macimorelin levels such as CYP3A4 inducers (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, armodafinil, rufinamide) leading to false positive results, carefully reviewing and discontinuing these medications (after approval following discussion with the prescribing physician while providing sufficient washout time prior to testing) is recommended. **Table 1** displays the individual characteristics of each GH stimulation test used in the United States and Europe.

2.2 Beneficial effects of rhGH replacement therapy

Previous studies have shown that rhGH replacement improved body composition, increased bone mineral density (BMD) and QoL, and decreased cardiovascular risk factors [2, 37]. Most of these beneficial effects are generally reported within the first year of therapy [38-42], with the exception for BMD changes. However, long-term rhGH therapy is not without its drawbacks **(Table 2)**. In young adults with persistent GHD transitioning over to adult services, early retesting of patients with idiopathic isolated GHD (i.e., before the achievement of final height and/or the adult pubertal stage) may avoid possible over-treatment [43] and prompt resumption of rhGH therapy to induce somatic development of body composition and bone maturation [44-46].

Several observational studies with at least 7 years of follow-up data have demonstrated that many clinical improvements of rhGH therapy in adults with GHD are sustainable with low prevalence of side-effects [14, 15, 47, 48], likely due to the increasing trend of using low non-weight-based rhGH doses [41, 42, 49]. In a study of adults with GHD with 15 years follow-up, Elbornsson et al. [14] reported improvements in lean mass and an initial decrease in fat mass, followed by a gradual increase over time, which may be related to aging. Conversely, the systematic review by Appelman-Dijkstra et al. [13] demonstrated that the long-term effects of rhGH therapy on BMI are not consistent (some studies showing an increase and others no change), while Spielhagen et al. [50] found that most long-term studies showed no changes on waist-hip ratio and one study showing waist circumference increase. It has been hypothesized that the observed BMI and waist circumference increase is caused by normal aging off-setting the overall

improvement of rhGH therapy on body composition [51]. The findings by Filipsson Nystrom et al. [52] reinforced this hypothesis when they found that after rhGH had been discontinued following more than three years of therapy, central adiposity increased and thigh muscle mass decreased. In a meta-analysis of 22 studies, Newman et al. [53] demonstrated that mean lean mass increased by 2.61 kg vs 0.04 kg, whereas fat mass decreased by 2.19 kg vs 0.31 in rhGH-treated and placebo-treated patients, respectively, with higher doses being more effective than lower doses.

Short-term rhGH studies have reported a 4-10% increase in BMD that is greater at the lumbar spine than femoral sites [54], and is more evident in males and in those with a lower baseline BMD. Females on estrogen tended to have a greater BMD increase compared to those not on estrogen, suggesting that adequate estrogen replacement is important to achieve an optimal BMD response in females with GHD [55]. Positive effects on bone microarchitecture was not observed [56], and initial vertebral BMD increases that was observed stabilized after 10 years of therapy [55]. Two recent meta-analyses have suggested that the beneficial effects of rhGH therapy on BMD was mainly influenced by gender, age, dose and treatment duration [57, 58], while in a 15-year follow-up study, Appelman-Dijkstra et al. [47] demonstrated sustained lumbar spine increase, femoral neck BMD stabilization, and unchanged incidence of fractures.

Treatment with rhGH therapy has also been shown to improve QoL in most adults with GHD, especially during the first year of treatment; an effect that may persist after 10 years of therapy [15, 16]. A retrospective analysis of patients treated with rhGH during childhood showed that QoL results are closely linked to the underlying indication for rhGH treatment. Patients with associated diseases or syndromes scored slightly lower,

especially cancer survivor patients compared to patients with isolated GHD or idiopathic short stature, and lower physical component summary was associated with lower educational levels [59]. These data imply the importance of acknowledging the etiology of adults with CO-GHD when interpreting QoL data. It is also noteworthy that improvements in QoL have not consistently been reported in all adults or in all assessed socio-psychological domains [60, 61]. Patients with worse baseline QoL were better responders than those with relatively normal baseline QoL [15, 16]. Additionally, there are other studies that have shown more limited improvements and no gender predisposition [61-63]. The Treatment-Related Impact Measure-Adult Growth Hormone Deficiency (TRIM-AGHD), a patient-reported outcome measure assessing GHD impacts, appears to be a highly responsive measure assessing adult GHD treatment impacts, with a 10-point change score being considered a clinically meaningful improvement [64]. However, caution still needs to be exercised in assessing the literacy level and understanding of the patient when using QoL questionnaires, and the data should be interpreted in the context of a detailed medical history.

Studies have also shown that rhGH therapy improved several cardiovascular markers, including lipids, visceral fat, and some echocardiographic parameters, including interventricular septum diameter, left ventricular posterior wall-diameter and left ventricular mass index [65-67], whereas discontinuing long-term rhGH therapy may worsen total- and LDL-cholesterol levels [52] and diastolic blood pressure [68]. Other surrogate cardiovascular risk markers have been shown to improve with rhGH therapy, including C-reactive protein [69, 70], adipsin [71], pro-inflammatory cytokines such as

tumor-necrosis factor alpha [72], pregnancy-associated plasma protein A [73], lipid peroxidation [74] decreased, and markers of endothelial dysfunction [75].

Age of the patient is an important determinant when implementing a rhGH dosing regimen. Older patients are more sensitive to rhGH therapy, hence more susceptible to side-effects. Acknowledging this notion, several consensus guidelines now recommend using low rhGH doses in older patients [11, 30, 76]. However, there are no data on the efficacy and safety of long-term rhGH replacement in patients above 80 years of age with GHD [77]. In a prospective, single-center, open-label study, the effects of rhGH replacement were assessed in 24 adults with GHD above 65 years of age and in 24 younger patients. Lower doses were used, yet greater reductions in waist/hip ratio and serum LDL-cholesterol levels were observed, with these differences being persistent after correction for duration of hypopituitarism, suggesting enhanced GH responsiveness with aging [78].

3. Effects of GHD on sleep, skin and coagulation

Growth hormone and IGF-I receptors are expressed in various tissues throughout the body. However, the effects of GH on skin, sleep, and coagulation system have not been well-studied, and in recent years, several studies have assessed the effects of rhGH therapy on these parameters. The effects of GH may be clinically relevant, as borne out by the effects of GH on the skin where excess GH in acromegaly causes skin thickening [79], on sleep where adults with untreated GHD report sleep disturbances [80], and on vascular functions, of which some are related to the regulation of coagulation processes [81-83].

3.1 Sleep

Sleep is characterized by cyclical periods of rapid eye movement (REM) and non-REM (NREM) sleep [84]. There is some evidence demonstrating bidirectional interactions between the GHRH/GH/IGF-I axis and sleep regulation [84], with GH preferentially secreted during sleep [85]. Early animal [86] and human [87, 88] studies have shown that GHRH exerts sleep-promoting effects and increases the duration and/or intensity of NREM sleep, despite the absence of GH, implying that increased hypothalamic GHRH secretion may enhance daytime sleepiness and fatigue. Due to lack of negative feedback inhibition by GH in adults with untreated GHD, hypothalamic GHRH secretion is increased [89]. In a study involving middle-aged men with GHD, Nolte et al. [90] demonstrated that rhGH therapy may influence sleep reaction, and a decrease in slow-wave sleep was observed upon cessation of therapy. In another study, Schneider et al. [91] did not find any differences in baseline sleep parameters of adults with GHD compared to healthy controls, and rhGH therapy did not affect total sleep time and time spent in different sleep stages. In a study by Peker et al. [92] of adults with GHD evaluating sleep architecture by polysomnography before and after 6 months of rhGH therapy, mean total sleep time, durations of low-wave sleep, and REM sleep were not altered, but a mild increase in REM sleep time in those with obstructive sleep apnea after 6 months of rhGH therapy was observed. Conversely, Ismailogullari et al. [93] did not observe any differences in sleep parameters using polysomnography to assess patients with Sheehan's syndrome before and after 6 months of rhGH therapy, while Morselli et

al. [94] reported that 4 months of rhGH therapy in adults with GHD induced a shorter sleep period time and decreased the intensity of slow-wave sleep.

In summary, current data suggest increased NREM sleep (mainly slow-wave sleep) and decreased REM sleep durations in adults with GHD compared to age/sex-matched controls, and these changes in sleep parameters may explain the impaired memory, increased daytime tiredness, and decreased QoL seen in these patients. However, the effects of rhGH therapy are indeterminate due to lack of long-term placebo-controlled studies, as short-term studies of rhGH therapy do not appear to fully reverse the disturbances in various sleep parameters.

3.2 Skin

It has been suggested that adults with GHD have decreased sweating and skin sebum content leading to dry skin and early aging of the skin [95]. Borlu et al. [96] investigated the skin characteristics in GH-deficient patients with Sheehan's syndrome, and found that skin capacitance decreased on the forehead and forearm, and the sebum content decreased on the forehead, but after 6 months of rhGH therapy, the same investigators found that sebum content on the forehead increased without any changes in skin capacitance [97]. The effects of rhGH on the skin has been particularly relevant in recent years because of its use increasing as an anti-aging agent [98]. Although rhGH treatment may enhance dermal collagen content thus increasing skin thickness, it should not be used as an anti-aging agent as there are no safety data [99]. However, because of the lack of good quality data, further studies of rhGH therapy on skin changes are still warranted.

3.3 Coagulation

Previous studies have shown that patients with hypopituitarism treated with other hormone replacement therapies but without rhGH exhibit increased cardiovascular and cerebrovascular mortalities in comparison with general population [3, 5]. Changes in the coagulation system are implicated for being responsible for the increased thromboembolic events [83]. Fibrinogen and plasminogen activator inhibitor-1 levels increased [81, 83], and tissue plasminogen activator decreased in adults with GHD [81], explaining their thrombotic tendency. Following rhGH therapy, fibrinogen, plasminogen activator inhibitor-1 and tissue plasminogen activator decreased [82, 100], fibrinolysis improved that was attributed to improvement of stimulated endothelial tissue plasminogen activator release in response to venous occlusion [101], protein S activity normalized and antithrombin and protein C activities decreased [102].

Despite improvement following rhGH therapy on the prothrombotic state, increased fibrinogen, factor VIII, and von Willebrand factor levels were still present [103]. Baseline prothrombin time and activated partial thromboplastin time levels were in the normal range and remained unchanged 6 months after rhGH therapy, while platelet numbers were unaffected either by GHD *per se* or by rhGH therapy [102]. In summary, coagulation and fibrinolysis may be adversely affected by GHD itself in favor of thrombosis, and rhGH therapy may partially reverse these abnormalities. More studies are needed to clarify the direct effects of rhGH rather than on secondary changes as a consequence of alterations in body composition or dyslipidemia on the coagulation system.

4. Side-effects of rhGH replacement therapy

Side-effects from rhGH therapy are mainly caused by its fluid retaining effects (e.g., edema, arthralgias, myalgias, paresthesias, and carpal tunnel syndrome), occur when high rhGH doses are used, and tend to resolve with dose reductions or treatment cessation. A recent randomized, open-label, clinical trial involving adults receiving GH therapy for at least 1 year showed that although increasing rhGH dose targeting IGF-I SDS between +1 and +2 improved waist circumference and mood, patients with higher serum IGF-I levels reported more myalgia, whereas those with lower IGF-I levels reported more fatigue [104]. In another study, the same investigators decreased the rhGH dose to target the IGF-I SDS between - 2 to - 1 or increased the rhGH dose to target the IGF-I SDS between +1 to +2 over a 24-week period. Females in the low dose group reported better working memory and strategic memory control compared to females in the high dose group, whereas females in the low dose group reported more fatigue and less vigor [105].

Treatment with rhGH, especially with high doses, decreases insulin sensitivity and induces glucose intolerance [68]. In the Hypopituitary Control and Complications Study, the prevalence and incidence of diabetes mellitus (DM) in adults treated with rhGH was analyzed [106]. Results of an analysis of 2,922 patients in the United States and 3,709 in Europe, with a mean follow-up of 4.1 years, showed that in the United States, the incidence rate of DM adjusted for age, sex, and BMI was higher in rhGH-treated patients than in the general population. In France and Germany, the incidence rates were comparable with the reference population, while in Sweden, the incidence rate was increased in rhGH-treated patients. In another analysis of 5,143 patients from the Pfizer International Metabolic Database (KIMS), with 20,106 patient-year follow-up, the

observed/expected cases ratio was 10.8 in the first year of rhGH treatment that decreased to 1.9 after 8 years of treatment. When the incidence of DM in patients in the KIMS study was compared with the incidence rates in age-adjusted populations in other United States and European regions, the observed/expected cases ratios ranged from 2.11 to 5.22 [107]. Conversely, a study of 245 patients with adult-onset GHD showed that more than 4 years of rhGH therapy did not negatively affect glucose homeostasis [108]. This was substantiated by a meta-analysis of 94 randomized controlled and open trials that failed to demonstrate any increased frequency of DM in the short-term placebo controlled trials and during long-term rhGH therapy [109]. The inconsistent evidence of long-term rhGH effects on glucose homeostasis may be due to lack of control data and the heterogeneity of large international studies. Thus, close monitoring of glucose parameters is important during rhGH treatment especially in obese patients or those with glucose intolerance, and to consider initiating low-dose treatment and cautiously titrate the dose upwards according to clinical response and serum IGF-I levels.

Previous studies have shown an increased cancer risk with rhGH replacement therapy [110], whereas others have not [111]. In a group of 6,840 adults included in the Hypopituitary Control and Complications Study, the incidence ratio of neoplasia was 0.88 (0.74–1.04), but rose to 3.79 (1.39–8.26) in patients younger than 35 years and to 2.74 (1.18–5.42) in patients with CO-GHD [112], suggesting that the overall risk of primary cancer in adult life was not increased. Child et al. [113] reported the incidence of primary neoplasia in 8,418 patients treated with rhGH, as well as in 3,668 GH-treated patients with history of pituitary adenoma and 956 rhGH-treated patients with history of craniopharyngioma. Comparisons carried out in cohorts of untreated patients, and during

a mean follow-up of 4.8 years, found no increased risk for all-site cancers, including breast, prostate and colorectal cancers, in rhGH-treated patients. In a meta-analysis of 15 studies involving 46,148 adults with GHD, rhGH therapy did not increase the risk of pituitary tumor recurrence (relative risk, 0.77; 95 % confidence interval, 0.53-1.13) and secondary malignancy (relative risk, 0.99; 95 % confidence interval, 0.70-1.39), but the risk for stroke was higher in untreated patients (relative risk, 2.07; 95 % confidence interval, 1.51-2.83), supporting the overall safety of rhGH therapy [114, 115].

Excess cardiovascular and cerebrovascular mortalities have been reported in previous epidemiological studies in patients with hypopituitarism, with GHD being implicated as one of the contributing factors [3-6, 48, 116]. Data from the Dutch National Registry of rhGH treatment [117] compared 2,229 patients treated with rhGH with an untreated control group of 109 and a secondary control group of 356 patients treated with rhGH in whom treatment had been discontinued. The standardized mortality ratio in relation to the general population was 1.27 (1.04–1.56) for the treatment group, and the ratio was 1.29 (1.05–1.59) when patients with acromegaly and Cushing's disease were excluded, and decreased to 1.00 (0.79–1.26) after the exclusion of high-risk patients (e.g., craniopharyngioma). Notably, the authors did not find any increase in mortality in the two untreated control groups. In another study by Gaillard et al. [116] of 13,983 rhGH-treated patients from the KIMS database followed up for 4.9 years, the authors showed that all-cause mortality was 13% higher than in the general population. Conversely, Olsson et al. [48] demonstrated in a study of 426 patients with nonfunctioning adenomas and nearly 4600 patient-years follow-up, of which 207 were treated with rhGH therapy and 219 were untreated, the overall mortality in the treated patients compared with the

general population and death due to malignancy was reduced. Because of possible selection bias in this study, rhGH therapy cannot be ascribed as directly responsible in increasing life expectancy and decreasing cancer risk, but does imply that long-term therapy is, at least, safe. These findings has been further substantiated in a recent large meta-analysis of 2 retrospective and 7 prospective studies involving 11,191 patients treated between 2.3 to 14.5 years demonstrating that rhGH therapy reduced cancer risk in adults with GHD [118], further reinforcing the safety of long-term rhGH therapy.

In children with GHD and a history of cancer, studies have demonstrated no increase in relative risk of recurrence of the primary tumor in rhGH-treated individuals [119, 120]. The relative risk of developing a subsequent tumor in rhGH-treated childhood cancer survivors is elevated by 2.15-fold (95% CI 1.3–3.5) [121]. Similar data on primary and secondary tumors have been reported from the Pfizer International Growth Database (KIGS) post-marketing study [122, 123]. However, it remains unclear whether the increased risk of secondary tumors was due to the inherent characteristics of those children receiving rhGH therapy. For example, when the estimates of the relative risk of subsequent central nervous system tumors were adjusted for the effect of radiation therapy, there was no increased risk associated with rhGH therapy [124]. The 2018 Endocrine Society Clinical Practice Guidelines suggest carefully offering rhGH treatment to childhood cancer survivors with confirmed GHD [125]. Nevertheless, rhGH therapy is contraindicated in patients with active malignancy [126], and should only be prescribed with caution to patients with a history of cancer and strong family history of cancer [127].

5. Growth hormone receptor polymorphisms and responsiveness to rhGH therapy

Growth hormone exerts its biological effects by binding to the GH receptor (GHR) on the cell membrane of target cells. The human GHR gene is located in chromosome 5 [128, 129], where there are 9 exons that encode the receptor and several additional exons in the 5′ untranslated region. There are two major isoforms of the GHR that differ by the absence of exon 3 that encodes part of the extracellular domain of the GHR. Its absence gives rise to a GHR lacking 22 amino acids in the extracellular domain [128, 129]. The isoform of human GHR containing exon 3 is known as the full-length isoform (fl-GHR) and the isoform without exon 3 as the exon 3-deficient isoform (d3-GHR). This polymorphism has been extensively studied since the loss of a complete exon from a gene without affecting the function of the resulting protein is uncommon, and the binding capabilities of the two GHR isoforms are considered somewhat similar [130, 131]. The d3-GHR isoform is dominant over the fl-GHR isoform and about half of Europeans are hetero- or homozygous with respect to the allele encoding the d3-GHR isoform [132].

Early studies demonstrated inter-individual variability of responsiveness to rhGH therapy, particularly in terms of metabolic parameters and hepatic IGF-I synthesis [133, 134]. Age, gender, BMI, genetic factors, GH binding protein levels, rhGH dose used appear to be contributing factors [135-137], whereas amongst genetic factors, GHR polymorphisms has been suggested to play a role in individual rhGH responsiveness. In adults with GHD, some studies have shown increased responsiveness in the carriers of d3-GHR allele [138-140] and others have shown opposite results [141-144]. **Table 3**

summarizes the main findings of the effects of d3-GHR polymorphism on responsiveness to rhGH therapy in adults with GHD.

Glad et al. [144] and Moyes et al. [139] reported that homozygote fl-GHR individuals had greater IGF-I responses than carriers of the d3-GHR genotype after rhGH therapy, while Meyer et al. [138] found that after 1 year of therapy, the required rhGH dose was lower in patients carrying one or two d3 alleles compared with those with the fl/fl genotype in achieving comparable serum IGF-I levels [138]. However, other studies have reported different response patterns. After 1 year of rhGH therapy, Barbosa et al. [143] found that baseline values and changes in IGF-I and body fat were similar between those with fl-HR alleles and those with at least one d3-GHR allele. Andujar-Plata et al. [142] corroborated these findings by demonstrating that the d3-GHR allele did not influence baseline serum IGF-I levels, adverse events or treatment discontinuation, while Adetunji et al. [141] reported no differences in the rhGH doses required to optimize serum IGF-I levels, QoL or body composition between carriers and non-carriers of the d3-GHR allele. Van der Klaauw et al. [140] found that serum IGF-I levels were higher in carriers of the d3-GHR allele compared with the fl/fl-GHR genotype and total cholesterol and LDL-cholesterol levels were lower in the group with at least one d3-GHR allele, whereas the increase in HDL-cholesterol was greater compared with non-carriers of the d3-GHR allele after 1 year, but these differential responses did not differ in all the GHR genotypes after 5 years of rhGH therapy [140]. Giavoli et al. [145] found that rhGH therapy normalized serum IGF-I levels and decreased body fat at 1 and 5 years, regardless of the presence of the d3-GHR allele. After 1 year, HDL-cholesterol increased in the d3-GHR carriers compared to non-carriers. After 1 and 5 years of therapy, the

number of subjects with impaired glucose tolerance that was similar in the two groups at baseline decreased in non-carriers and increased in d3-GHR allele carriers. In the d3-GHR carrier group, reductions in total and LDL-cholesterol were observed after 5 years of therapy. More recently, Bianchi et al. [146] reported that low dose rhGH therapy induced greater increases in serum IGF-I levels in the d3-d3 group in the short-term, and improved lipid profiles, fat mass and blood pressure in the d3-GHR carriers after short- and long-term rhGH therapy. In summary, only a few studies have convincingly demonstrated the role of GH receptor polymorphisms in affecting rhGH responsiveness in the treatment of adult GHD in increasing IGF-I and altering lipid profiles and glucose tolerance, suggesting that its effect is at best probably minimal without major clinical ramifications.

6. Adherence to growth hormone treatment

High rates of non-adherence have been reported by several studies in children with GHD on rhGH therapy; nevertheless empirical evidence is limited in the respective adult patient population. Two systematic reviews which analyzed a total of 19 studies involving children receiving rhGH therapy have found that the prevalence of non-adherence in children ranged from 71% (poor adherence defined as >85% or >1 missed injection/week) to less than 7% (excellent adherence) [147, 148].

Our literature search on the PubMed, Medline, CINAHL, EMBASE and PsychInfo databases to identify empirical studies which evaluated the prevalence of non-adherence to rhGH therapy in adults with GHD revealed five relevant studies involving a total of 509 patients [149-153]. These studies suggest an overall good adherence rate that

ranged between 70% and 91.3% of patients that missed less than one rhGH injection per week [149-153]. Adherence was measured via the number of rhGH prescription refills [152], an electronic auto-injector device [153], or self-reported adherence [149-151]. However, a characteristic finding is the high treatment discontinuation rate in adults with GD that varied between 13.3% [149], 17% [154], 21% [151] 50.8% [153] and 58.9% [152]. Common reasons for discontinuation of therapy reported in these studies were related to the patient's decision mainly due to lack of their awareness regarding rhGH health benefits and the perceived effects on health status and QoL, treatment re-evaluation purposes, side-effects, low adherence, and lapses of medical insurance coverage. Low persistence, defined as long treatment breaks or "drug holidays" lasting from a month to a year, was reported in 48% of non-adherent adult patients who reported being skeptical and less convinced of the benefit of their rhGH therapy [149]. Interestingly, Auer et al. [152] found a decrease of 9.8% in adherence between the first and second year of treatment, with 12.8% of patients being lost to follow-up.

Medication-taking behavior is complex, personal, and at times not exclusively the responsibility or within the control of the patient. Practical barriers affecting adherence common to adults and children receiving rhGH include forgetfulness, "injection fatigue", failure to renew the prescriptions and need for frequent refills, dissatisfaction with treatment outcomes (e.g., growth velocity in children, and health status and QoL in adults), treatment cost, shortage or limited choice of rhGH, lack of communication and inadequate contact with the endocrine specialist nurse and endocrinologist, lack of understanding of the treatment and condition, travelling, and being away from home [147-151, 155-159]. Perceptual barriers have also been associated with non-adherence

and include concerns about long-term complications and lack of perceived benefit of the rhGH treatment, embarrassment or peer pressure especially in adolescence, misconceptions about consequences of non-adherence, and lack of perceived true effectiveness of rhGH treatment [147-151, 155, 159-161]. Lower socio-economic and educational status are also important factors contributing to non-adherence [149, 159]. Interestingly, of the patients who had discontinued rhGH, 62.6% restarted treatment after a mean cessation period of 4.8 years [152], supporting the hypothesis that some patients only realize the true benefits from rhGH therapy retrospectively.

It is important that clinicians remain alert to some of the 'red flags' that may impact adherence, such as history of poor attendance at consultations. They should proactively engage the patient by adopting an open, co-operative, non-judgmental shared decision-making approach to develop an easy-to-follow rhGH treatment plan for both the patient and their families and/or caregivers [160]. In addition, it is also imperative to support the patient by setting realistic expectations for their treatment regarding health outcomes and to provide a clear rationale as to why they are treated with rhGH. Encouraging patients to maintain a diary or complete QoL questionnaires periodically may assist with treatment monitoring and provide positive reinforcement [162]. Clinicians can also recommend helpful practical strategies to the patient that include setting up reminders and provide longer prescription durations. The type of injection device has also been associated with greater adherence when it is selected to meet the individual patient needs, such as using needle-free device for those with needle phobia [163, 164], using user-friendly electronic auto-injector devices [165-167], and prescribing non-refrigerated rhGH brands [158, 168]. Similarly, patient satisfaction with care services

and effective clinician-patient rapport and frequent communication have been shown to improve adherence [169-171]. In support of this notion, Wickramasuriya et al. [172] demonstrated high adherence rates of over 95% for children who attended a multidisciplinary endocrine center with access to a nurse-led clinic that offered individualized rhGH treatment initiation. **Figure 1** presents a recommended algorithm which can support clinicians and patients in the shared-decision making process to select the most suitable device for each individual patient's needs [162].

7. Long-acting GH preparations

Many pharmaceutical companies have been developing LAGH preparations in the hope of improving treatment adherence and potentially treatment outcomes, while preserving safety and efficacy profile using fewer injections. Several different technologies have been used to render the GH molecule long-acting [173-175], and they include depot formulations, PEGylated molecules, pro-drug compounds, GH molecule non-covalently bound to albumin, GH molecule bound to Fab antibody, and GH fusion proteins. None are currently approved by the FDA, and **Table 4** displays the LAGH preparations currently under development.

Following the publication of the study by Lippe *et al.* [176] in 1979 using a depot GH preparation in gelatin solution, the next LAGH preparation that was developed was somatropin (rDNA origin), which was micronized zinc-stabilized GH encapsulated in microspheres (Nutropin Depot). Since then, other LAGH preparations have been developed and evaluated, namely LB03002 [177-184], Jintrolong [185, 186], Somapacitan (NNC0195-0092) [187, 188], ARX201, NNC126-0083 [189-192], PHA-

794428 [193, 194], Somavaratan (VRS-317) [195, 196], TV-1106 [197, 198], ALTU-238, TransCon GH (ACP-001) [199-202], GX-H9 [203], LAPSrhGH/HM10560A, MOD-4023 [204-208], CP016, BBT-031, ProFuse GH, and AG-B1512, with phase 2 and 3 studies that primarily assessed longitudinal growth in children and changes in body composition in adults as main primary endpoints [178, 179, 182, 186, 195, 209, 210]. Among them, LB03002 has been approved in South Korea and Europe, but has had limited marketing thus far, and Jintrolong has been approved and is used in children in China, whereas CP016, BBT-031, ProFuseGH, and AG-B1512 are still undergoing pre-clinical studies. In December 2016, Opko Biologics reported that the primary end-point change in trunk fat mass in adults with GHD from baseline to 26 weeks in a phase 3 study failed to demonstrate any difference between treatment with MOD-4023 and placebo [211]. Further plans to submit a pre-biologics license application by OPKO Biologics in collaboration with Pfizer to the FDA are underway, with additional studies being planned in adults using a pen device [211]. In September 2017, Versartis, Inc., the manufacturer of Somavaratan (VRS-317), announced that the drug failed to meet its primary end-point for non-inferiority comparison against daily Genotropin for height velocity in children (9.44 cm *vs* 10.70 cm for those receiving daily rhGH) in the VELOCITY phase 3 clinical trial. All clinical trials were suspended and Somavaratan was withdrawn from the United States Investigational Drug Application and equivalent filings in other countries [212]. Other LAGH preparations have also been discontinued for the following reasons: ARX201 due to the discovery of PEGylated-containing vacuoles in the epithelial cells of the choroid plexus in monkeys [173, 174], NNC126-0083 related to unsatisfactory IGF-I profiles at the doses administered [173, 174], PHA-

794428 due to high rates of injection-site lipoatrophy, particularly in women [193, 213], TV-1106 due to unfavorable benefit *vs* risk profile and the unlikelihood of gaining regulatory approval [173, 174], and ALTU-238 because the manufacturer declared bankruptcy [173, 174]. While several LAGH preparations are no longer being developed, the efficacy and safety of other LAGH preparations such as TransCon GH ACP-001, GX-H9, LAPSrhGH/HM10560A, MOD-4023, Somapacitan and Jintrolong in adults and children appear promising and are still currently being evaluated. The recently presented data of the phase 3 heiGHt trial demonstrated that annualized height velocity after 1 year of TransCon GH in untreated children with GHD was greater than daily rhGH injections (11.2 cm vs 10.3 cm; $P = 0.0088$) [202], whereas studies in adults with GHD are currently planned to start in 2020. On the other hand, the completed phase 3 [214] and ongoing extension study [215] in adults with GHD have demonstrated that weekly Somapacitan achieved IGF-I SDS values and maintained reductions in truncal fat that is similar to daily rhGH with a comparable safety profile, and was considered more convenient by the study participants.

However, questions have arisen as to whether LAGH preparations are as effective and safe compared to daily rhGH because they are not physiologic and varying pharmacokinetics and pharmacodynamics with each individual preparation. It could be argued that none of the currently available rhGH preparations used to treat GHD in children and adults are truly physiologic, because they are administered as single daily doses, rather than in a pulsatile fashion. It is noteworthy that there are several hormones administered as commercially-available long-acting preparations do not mimic normal pulsatile physiology, such as testosterone, medroxyprogesterone, and gonadotropin-

releasing hormone. Additionally, other types of medications frequently used by endocrinologists have been developed as long-acting preparations, such as once or twice weekly cabergoline rather than once to three times daily bromocriptine for hyperprolactinemia, bi-weekly testosterone cypionate injections, and ultra-long acting anti-resorptive medications, such as annual intravenous zoledronic acid infusions for osteoporosis. Other key questions include when is the optimal time to measure serum IGF-I levels, or whether other methods of assessing IGF-I, such as calculating the IGF-I area under the curve, and/or measuring other surrogate markers can be used reliably. It is also important to avoid causing supra-physiological IGF-I levels for too long in between injections [173], as this may theoretically induce "iatrogenic acromegaly", tumor recurrence, neoplasia and glucose intolerance. The question about timing of when to measure serum IGF-I levels does not arise with daily rhGH injections because serum IGF-I levels stabilize over a few days, hence measurement of that hormone at random times during therapy can been used to guide dosing, but with LAGH preparations, serum IGF-I levels may fluctuate across days to weeks between injections. It remains to be determined whether the dose of LAGH preparations should be titrated based on the type of LAGH used and the nadir, peak, or mean of several IGF-I measurements during therapy.

8. Expert commentary and 5-year view

Recombinant human GH replacement has been shown to exert beneficial effects, regardless of the underlying etiology of GHD, and its long-term use appears to be safe. However, rhGH therapy has not definitively been proven to improve overall mortality,

bone fractures, or cardio/cerebrovascular disease. The appropriate utilization of rhGH requires the identification of patients with a high pretest probability of adult GHD and confirmation of the diagnosis before therapy initiation. Following its approval by the FDA and EMA, the utilization of macimorelin is expected to increase over time as the preferred diagnostic test for adult GHD because the test is simple to perform, highly reproducible, safe, and has better tolerability compared to the ITT and GST. However, further studies with larger numbers of patients, including children, adolescents, elderly, and those with obesity, DM, traumatic brain injury, cranial irradiation, subarachnoid hemorrhage, and renal or hepatic diseases, are needed to determine the sensitivity and specificity of this agent in these patient cohorts. Additionally, studies are needed to improve the palatability of this drug, especially for children, and to help outline any other potential drug-to-drug interactions.

Results for clinical endpoints such as bone fractures, cardio/cerebrovascular disease, cancer and mortality, including those from large international databases and those with GH polymorphisms, should be interpreted with caution since all of them have diverse study designs and methodological flaws. What is well-recognized from published data is that rhGH therapy can improve and reverse many metabolic and psychological abnormalities associated with adult GHD, although some patients may benefit more than others. Clinical practice guidelines for monitoring efficacy and safety are well-established and have been previously published by several professional organizations [11, 20]. Long-term observational studies involving large numbers of patients have shown that many benefits of rhGH therapy are sustainable with a low frequency of side-effects, and an emphasis of using low individualized rhGH doses, especially in “susceptible” patients

(e.g, elderly, obese, and patients with underlying glucose intolerance).

Non-adherence and low persistence to rhGH injections remains an ongoing concern and limiting factor to good clinical outcomes. Unlike in children, the benefits of rhGH is harder to measure in adults which may impact on their ability and willingness to persist with treatment. Many barriers to good adherence can be overcome by the clinician with counselling and maintaining good relationship with the patient, and delivering useful and clear education and training soon after diagnosis. Emphasis should be given on individualized treatment planning and ensuring that patients have a clear understanding of the rationale for their treatment.

The ongoing development of LAGH preparations aims to reduce the number of injections and may potentially improve treatment adherence and outcomes. Further prospective studies and long-term surveillance studies after any regulatory approval of LAGH preparations are recommended for assessing long-term efficacy, safety, tolerability and cost-effectiveness, and to help better understand the effects of prolonged exposure to these compounds [173]. We encourage endocrinologists to monitor developments in this arena as FDA and EMA submission(s) are anticipated to be filed in the near future. Nonetheless, although more research is needed in some key areas, recent clinical advances have allowed us to improve our understanding on a number of clinically relevant issues in better managing adults with GHD.

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KEY POINTS

- Since adult growth hormone deficiency (GHD) has been characterized as a clinical entity, the effects of recombinant human GH (rhGH) replacement therapy have been extensively evaluated. Improvements in most, but not all, metabolic and psychological abnormalities associated with this condition have been demonstrated. Recent long-term studies have suggested that most of the beneficial effects of rhGH therapy are sustainable long-term, but not without some drawbacks.
- Diagnosis of adult GHD often requires performing GH stimulation testing. The utilization of the newly approved oral macimorelin test in the United States and Europe will likely increase over time because the test is simple to perform, highly reproducible, well-tolerated and safe. The lower GH cut-point of 2.8 μg/L was selected by the United States Food and Drug Administration as the cut-point; however, the GH cut-point up to 5.1 μg/L may also be considered because it increases the sensitivity of the test while maintaining its specificity to the GH cut-point of 2.8 μg/L.
- Age of the patient is an important determinant for rhGH dose initiation, and maintenance with lower doses is emphasized for older patients.
- Treatment with rhGH therapy has been shown to improve health-related quality of life (QoL) in most adults with GHD, and those with worse baseline QoL generally responded better than those with relatively normal baseline QoL.
- Due to the presence of GH and IGF-I receptors throughout the body, the effects of rhGH therapy on skin, sleep, and coagulation system in adults have been

investigated in greater detail in recent years. Decreased sweating and skin sebum content causing dry skin and early skin aging, decreased REM sleep, increased slow wave sleep which may contribute to impaired memory functions, and impaired coagulation and fibrinolysis have been reported in adults with GHD, and rhGH replacement therapy has been shown to reverse some of the abnormal parameters affecting the skin, sleep pattern, and coagulation system.

- Previous studies have consistently shown that treatment with rhGH may worsen insulin resistance, but recent large observational studies have demonstrated conflicting data. Some studies have suggested that the incidence rate of diabetes mellitus (DM) was persistently increased, while others have shown no increase in the frequency of DM with long-term rhGH therapy. Close monitoring of glucose parameters remains essential during rhGH treatment especially in "at risk" patients (e.g., patients with obesity or glucose intolerance).
- Previous data on cancer risk with long-term rhGH replacement therapy has been inconsistent, with some studies suggesting an increased risk and others demonstrating a neutral effect, or even decreased risk. Therefore, definitive conclusions regarding the risk of cancer induction with rhGH therapy cannot be drawn, but existing data suggest that long-term rhGH therapy is safe.
- Increased mortality has been reported in previous epidemiological studies in patients with hypopituitarism, with GHD being implicated as one of the contributing factors. Some of the recently published large observational studies have shown that rhGH therapy increased mortality rates, whereas others have

demonstrated that the overall mortality in the treated patients compared with the general population was significantly reduced. Because of the heterogeneity of patients and selection bias of some results cannot be excluded, firm conclusions at this point cannot be drawn on the effects of long-term rhGH therapy on mortality rates in adults with GHD.

- Previous systematic reviews and meta-analysis in adults with GHD have shown that d3-GHR isoform may exert a weak influence on therapeutic response to rhGH, but data are heterogeneous and inconsistent likely because most studies involved small numbers and were not designed to address the question of GHR genotype-genotype relationships.
- Studies suggest that adults with GHD report low persistence with rhGH therapy and high discontinuation rates, which are mainly associated poor understanding and perceived benefit of treatment. Although many factors can impact adherence to rhGH treatment, non-adherence can be minimized through shared decision-making and a personalized treatment plan at rhGH initiation.
- Long-acting GH preparations represent an advancement over daily rhGH injections because of fewer injections that may offer increased acceptance, tolerability, and therapeutic flexibility to patients that potentially can improve treatment outcomes. However, given the non-physiological profile of LAGH preparations, long-term surveillance are needed to assess for efficacy and safety that will be essential for understanding the impact of prolonged exposure to these compounds.

Table 1 Accepted GH cut-points for GH stimulation tests commonly used in the United States and Europe to diagnose adult GHD.

	GH cut-points (μg/L)	Comments
ITT	< 3.0 to 5.0	- Requires close medical supervision throughout the test due to concerns for hypoglycemia - May be unpleasant and cautioned in some patients because of potential side-effects (e.g., seizures or loss of consciousness resulting from neuroglycopenia), and contraindicated in the elderly and patients at risk for cardio/cerebrovascular disease - Patents with insulin resistance may fail to achieve adequate hypoglycemia because of underlying insulin resistance, requiring the use of higher insulin doses (0.15-0.2 IU/kg), thus increasing the risk of delayed hypoglycemia - Although the ITT demonstrates good sensitivity, its reproducibility is another limitation
Glucagon - BMI < 25 kg/m^2 - BMI 25-30 kg/m^2 - BMI ≥ 30 kg/m^2	 ≤ 3.0 ≤ 1.0 ≤ 1.0	- Advantages of the test include reproducibility, safety, and lack of influence by gender and hypothalamic GHD - Disadvantages include the long duration of the test (3-4 hours), intramuscular injection and relatively common side-effects that include nausea, vomiting, and headaches ranging from < 10% to 34% - Cautioned in the elderly, where severe symptomatic hypotension, hypoglycemia and seizures have been reported
Macimorelin	≤ 2.8	- First oral GH secretagogue - Approved for use as a diagnostic test in the United States and Europe - Showed good discrimination comparable to GHRH plus arginine and ITT - Simple, highly reproducible, well-tolerated and safe - The FDA selected a low GH cut-point of 2.8 μg/L, but using a higher GH cut-point of 5.1 μg/L was still able to correctly identify all GH-deficient patients without misclassifying those that were GH-sufficient
GHRH-arginine - BMI < 25 kg/m^2 - BMI 25-30 kg/m^2 - BMI ≥ 30 kg/m^2	< 11.0 < 8.0 < 4.0	- Transient facial flushing may occur after administration of recombinant GHRH - Recombinant GHRH not available in the United States, but still available in Europe
Arginine	≤ 0.4	- Weak GH secretagogue, requiring very low GH cut-point - Side-effects uncommon, but 5-10% of subjects reported paresthesias, dry mouth and headache - Not recommended for use unless no other GH stimulation tests are available

BMI, body mass index; FDA, Food and Drug Administration; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; ITT, insulin tolerance test.

Table 2 Summary of benefits and drawbacks of long-term rhGH therapy in adults with GHD.

Parameters	Benefits	Drawbacks
Body composition	- ↓fat mass and ↑lean mass	- ↑fluid weight
Bone metabolism	- ↑bone mineral density	- Future fracture rates not conclusively proven
Quality of life	- Improved QoL, especially in patients with very poor pre-treatment QoL	- Improvement in some dimensions of QoL not consistently shown - ↔ QoL in some patients, especially in patients with relatively normal or mild baseline QoL
Cardiovascular and metabolic risk factors	- ↑conventional risk factors (e.g., lipids and blood pressure) - ↑surrogate risk factors (e.g., carotid intima-media thickness, C-reactive protein, pro-inflammatory cytokines, adipokines, pregnancy-associated plasma protein A, pro-coagulative factors, and endothelial dysfunction) - ↑myocardial diastolic function	- ↑insulin resistance and ↑glucose intolerance - ↑risk of congestive heart failure due to fluid retentive effects, but this risk is small
Neoplasia	- ↔overall risk of hypothalamic-pituitary tumor recurrence or progression and overall risk of induction of malignancy	- ↑risk of secondary neoplasia in childhood cancer survivors, especially in those previously treated with cranial irradiation, but this risk is small
Mortality	- possible ↓risk of global and cardiovascular mortality in patients with hypopituitarism	- ↓mortality rates not conclusively proven

↑, increased; ↓, decreased; ↔, unchanged; QoL quality of life.

Table 3 Summary of studies investigating the effects of d3-GHR polymorphism and responsiveness to rhGH therapy in adults with GHD.

	Genotype, %						
Studies	***n***	*fl-fl*	*d3-fl*	*d3-d3*	*d3-carriers*	**Outcomes investigated**	**Main findings**
Meyer, et al. [138]	133	59	37	4	41	rhGH dose, IGF-I and SDS values, and anthropometry after 12 months of therapy	~25% lower rhGH dose needed to attain comparable IGF-I in *d3-carriers*
Moyes, et al. [139]	194	52	39	9	48	IGF-I and clinical signs and symptoms after 12 months of therapy	Minimal increase in IGF-I levels in the *d3-d3* group
van der Klaauw, et al. [140]	99 53	56	38	6	44	IGF-I, lipids, anthropometry, and bone mineral density after 1 and 5 years of therapy	*d3-carriers* had greater increase in IGF-I, lesser decrease in total and LDL-cholesterol, and greater increase in HDL-cholesterol No effect after 5 years of therapy
Adetunji, et al. [141]	131	55	39	6	45	Symptoms, quality of life and body composition after > 1 year of therapy	No effect after therapy
Andujar-Plata, et al. [142]	44	63	31	6	37	Baseline IGF-I, adverse events and treatment discontinuation after 6, 12 and 36 months of therapy	No effect at baseline
Barbosa, et al. [143]	124	58	30	12	42	Baseline IGF-I, and total body fat mass and changes after 12 months of therapy	No effect at baseline
Glad, et al. [144]	313	59	35	7	41	Short (1 week) and long-term (6 and 12 months) IGF-I response to therapy	Greater IGF-I response at 1 week in the *fl-fl* group
Giavoli, et al. [145]	100 50	48	45	7	52	IGF-I, BMI, body composition, lipids, glucose homeostasis after 1 year (*n*=100) or 5 years (*n*=50) of therapy	No effect at baseline Higher increase of HDL-cholesterol and fasting glucose in d3-carriers after 1 year of therapy Lower number of patients with impaired

							glucose tolerance in *fl/fl*, but more in *d3-GHR* patients after 1 and 5 years of therapy Greater decrease in total and LDL-cholesterol in *d3-carriers* after 5 years of therapy
Bianchi, et al. [146]	69	54	33	13	0	Short- (6 and 12 months) and long-term (5 years) IGF-I, anthropometry, lipids, glucose homeostasis, and blood pressure responses to low dose (0.01-0.03 mg/kg/week) therapy	Higher increase of IGF-I in the *d3-d3* group after 6 and 12 months of therapy; *d3-carriers* showed a more effective short- and long-term response with respect to LDL-cholesterol, fat mass and blood pressure reductions

BMI, body mass index; GHR, growth hormone receptor; HDL, high-density lipoprotein; IGF-I, insulin-like growth factor I; LDL, low-density lipoprotein; rhGH, recombinant human growth hormone; SDS, standard deviation score.

Table 4 Overview of LAGH preparations currently studied and under development.

Technology used	Product (Company)	Modification to the GH molecule	Frequency of administration	Current status
Depot	LB03002 (LG Life Sciences, Ltd)	Microparticles containing GH incorporated into sodium hyaluronate and dispersed in an oil base of medium-chain triglycerides	7 days	Approved and marketed in South Korea for childhood GHD. Approved but not marketed in Europe.
Depot	CP016 (Critical Pharmaceuticals)	Supercritical carbon dioxide, formed when carbon dioxide exceeds its thermodynamic critical point, used to create the depot	14 days (planned)	Pre-clinical studies
PEGylated	BBT-031 (Bolder Biotechnology)	Site-specific PEGylated GH analog	7 days (planned)	Pre-clinical studies
PEGylated	Jintrolong (GeneScience Pharmaceuticals, Ltd)	40-kDa PEG linked to GH	7 days	Approved in China for childhood GHD
Prodrug	TransCon ACP-001 (Ascendis)	GH transiently linked to carrier molecule via a self-cleaving linker, and releases GH unmodified	7 days	Phase 3 in children completed and presented, phase 3 in adults in planning stages
GH molecule bound to albumin	Somapacitan NNC0195-0092 (Novo Nordisk)	Single point mutation in GH, with non-covalent albumin binding moiety attached	7 days	Phase 3 in children, phase 3 and extension study in adults
GH molecule bound to Fab antibody	AG-B1512 (Ahngook Pharmaceutical Co., Ltd.)	Recombinant human GH genetically fused to a polypeptide linker and an anti-HSA Fab antibody	14-28 days (planned)	Pre-clinical studies
GH fusion protein	ProFuse GH (Asterion)	GH-binding protein	1 month (planned)	Pre-clinical studies
GH fusion protein	GX-H9 (Genexine, Inc. and Handok, Inc.)	Hybridization of non-cytolytic immunoglobulin Fc portion of IgD and IgG4	7-14 days	Phase 2 in children and adults, pending phase 3 trial in adults
GH fusion protein	LAPSrhGH/HM10560A (Hanmi Pharmaceutical Co., Ltd.)	Homodimeric aglycosylated IgG4 Fc fragment	7-14 days	Phase 2 in children and adults
GH fusion protein	MOD-4023 (Pfizer, Inc.)	Carboxyl-terminal peptide of hCG β-subunit	7 days	Phase 3 in children, phase 3 in adults failed primary end-point and further studies planned for pen devices

Fab, fragment antigen binding; Fc, fragment crystallizable; GHD, growth hormone deficiency; hCG, human chorionic gonadotropin; HSA, human serum albumin; IgD, immunoglobulin D; IgG, immunoglobulin G; PEG, polyethylene glycol.

Figure 1: Algorithm for selecting a suitable GH injection device patient's individual needs (used with permission from Llahana et al, 2019).