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REVIEW

Treatment of adult growth hormone deficiency with human recombinant growth hormone: an update on current evidence and critical review of advantages and pitfalls

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Abstract Adult-onset growth-hormone (GH) deficiency (GHD) is a rare disorder, which most commonly results from pituitary or peripituitary tumors and their treatment, and is characterized by alterations in body composition, carbohydrate and lipid metabolism, bone mineral density, cardiovascular risk profile and quality of life, all of which may contribute to an increased morbidity and mortality. Since recombinant human GH (rhGH) became available in 1985, several studies have provided evidence of its beneficial effects, despite the potential risk of developing adverse effects, and much clinical experience has been accumulated. However, in adults, the precise therapeutic role of GH replacement therapy and the individual response to it remains highly variable and is still a matter of debate. In this article, we present a critical review of the available evidence on rhGH replacement therapy in GHD adults, emphasizing the pitfalls clinicians encounter in the diagnosis of GHD and monitoring of rhGH replacement therapy. We will cover all the relevant aspects regarding the potential usefulness of GH treatment, including the hot topic of mortality.

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Introduction

Growth hormone (GH) deficiency (GHD) is a rare disorder which may occur during childhood or develop later in life. Childhood-onset GHD is most commonly idiopathic and is not necessarily associated with other pituitary hormone deficiencies, whilst adult-onset GHD most commonly results from pituitary or peripituitary tumors and their treatment [1]. Despite its relative rarity, GHD contributes to an increased morbidity and mortality, and a correct diagnosis is essential to be able to establish GH replacement therapy. We will hereon focus on adult GHD.

Since recombinant human GH (rhGH) became available in 1985, several studies have provided evidence of its beneficial effects, despite the potential risk of developing adverse effects, and much clinical experience has been accumulated. However, in adults, the precise therapeutic role of GH replacement therapy and the individual response to it remains highly complex and variable, and is still a matter of debate [1–3]. Moreover, reductions in cardiovascular events and mortality have yet to be demonstrated [4].

In this article, we present a critical review of the available evidence on GH replacement therapy in GH-deficient adults, emphasizing the pitfalls clinicians encounter in the diagnosis of GHD and monitoring of GH replacement therapy. Is GH treatment truly useful? How, when and to whom should it be prescribed? How can we decide if a patient should be treated with GH replacement therapy? In this regard, and as for any other hormonal deficiency, we hereby try to provide answers to specific questions, and thus be able to decide whether or not to begin a replacement treatment.

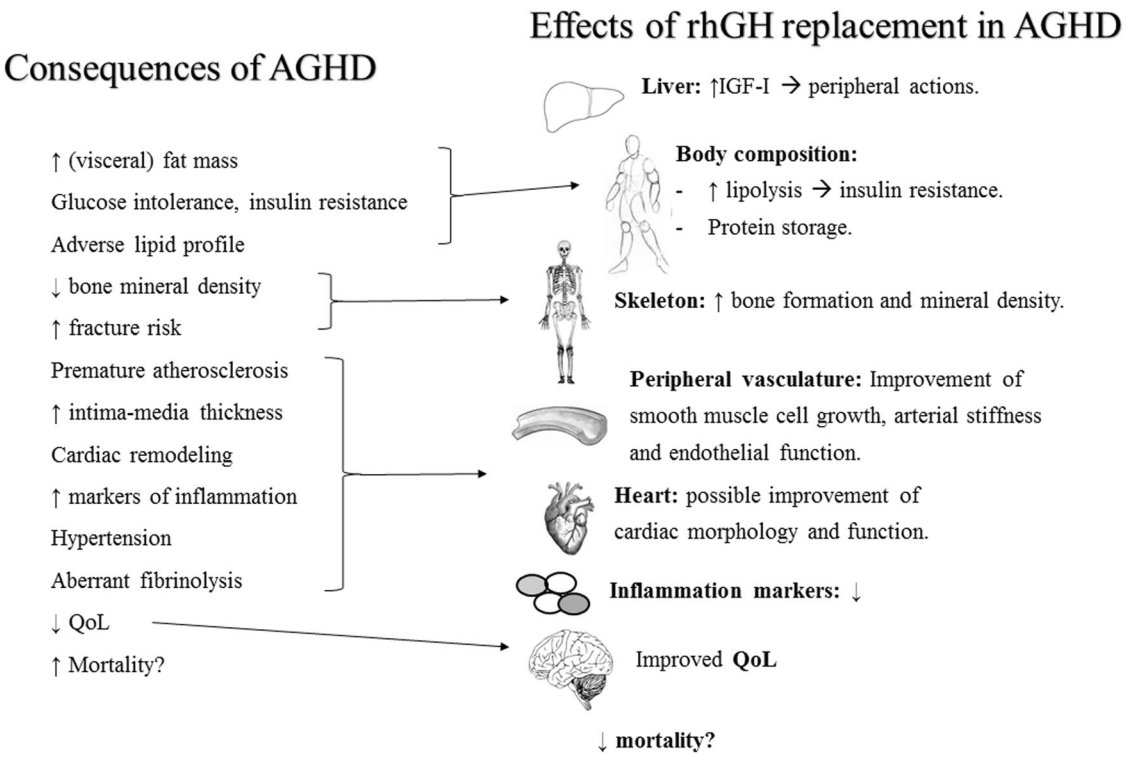

Fig. 1 Schematic representation summarizing the main consequences of GH deficiency in adults (AGHD) and the main actions of recombinant human growth hormone (rhGH) treatment. ↑ increases, ↓ decreases, QoL quality of life

Is GH deficiency clinically relevant?

Adult GHD entails alterations in body composition, with reduced bone and muscle mass and increased visceral and abdominal adiposity, diminished aerobic exercise performance and heart capacity, adverse changes in lipid and carbohydrate metabolism, increased rates of hypertension, increased intima-medial wall thickness, aberrant fibrinolysis, premature atherosclerosis and cardiac remodeling, increased markers of inflammation, reduction of bone mineral density, and increased risk fracture [5]. In addition, adult GHD has been associated to impaired cognition and psychological impact, leading to a decreased quality of life (QoL) [6] (Fig. 1).

Patients with hypopituitarism exhibit an increased mortality in comparison to control population, with standard mortality rates (SMR) ranging between 1.2–3.36 for male patients, and 1.3–4.54 for females, for all causes, but more specifically for vascular, cardiovascular and cerebrovascular diseases [7]. It must be remarked, however, that the SMR measures the number of observed deaths in a study population in comparison to the expected in general population, but does not consider other variables that could also impact mortality. Thus, further internal analysis of risk ratios within cohorts should be performed to serve as a better mortality indicator [8]. Also, analysis of mortality in GHD and hypopituitary patients may be complex and challenging due to the retrospective nature of many studies; the potential insufficient accuracy in the reported cause of mortality because data are usually based on death certificates, rather than on postmortem findings; the underlying etiology; potential associated pituitary deficiencies; previous treatments received (surgery, radiotherapy); likely insufficient control of cardiovascular risk factor in the past; or even the possibility of supraphysiological doses of replacement treatments, mainly glucocorticoids [7].

In any case, the reasons for an increased mortality in hypopituitary patients seem multifactorial [9–12], and GHD may be one of the main contributors [7]. Despite the fact that some benefits have been observed if defects on the somatotropic axis are present [13], we can indeed say that GHD in adults is clinically relevant, and that treatment should be aimed.

Can we diagnose GH deficiency in a reliable way?

The increasing public awareness of adult GHD and enhanced access to rhGH treatment today requires rigorous criteria for diagnosing GHD in adults. There are several clinical settings which entail a higher probability of developing GHD in adults. For instance, patients with macroadenomas, especially those which are invasive, compression of the pituitary portal system, sellar lesions, pituitary

surgery or radiotherapy, associated pituitary deficiencies, brain trauma or subarachnoid hemorrhage, frequently associate proven GHD, and a proactive diagnosis is usually recommended [9–12]. Isolated GHD is rare; in fact, it occurs in 7% of adult onset GHD, and is usually a consequence of cranial irradiation. It is usually the first deficit followed by other deficiencies, depending on the radiation dose and time from radiation. GHD was also frequently diagnosed in obese patients (functional GHD) in US databases. On the contrary, idiopathic GHD in adults is much rarer, and stringent criteria are recommended in order to avoid over or under diagnosis [4]. In this regard, current guidelines recommend using two GH-stimulation tests before making the diagnosis of GHD [4]. Severe GHD is diagnosed when peak GH values after an insulin tolerance test (ITT) are below 3 mcg/L. This cutoff was obtained according to the results of ITT in patients with multiple pituitary hormone deficiencies [14].

Indeed, GHD diagnosis may be jeopardized by several factors, including the absence of a clinical objective parameter (as opposed to children, in which growth velocity can be monitored), its unspecific phenotypic alterations, which frequently resemble normal aging, and the occasional overlap in serum hormonal levels between healthy controls and patients with mild GHD [15]. Moreover, GHD may be the first hormonal axis to be subtly affected in pituitary diseases, and a prompt diagnosis may be delayed. To make matters worse, laboratory evaluations are not always as accurate and reliable as one would wish for; in fact, determining hormones such as GH, which exhibit a pulsatile secretion and a high variability according to age, sex, body mass index, nutritional status, stress or exercise, may be cumbersome and subject to methodological errors [16]. Significant shifts in diagnostic patterns have occurred since the approval of the adult GHD indication: a trend to less severe forms of GHD, and thus, the pitfalls Therefore, pretest probability of GHD gains relevance in the evaluation of a potential case of GHD, and testing should be reserved for those patients with a high clinical suspicion, who are the ones that will benefit the most from GH replacement therapy. It is beyond the scope of this review to fully discuss the most commonly used GH stimulation tests (for further reports on GHD diagnostic tests see ref. [15], and reference [17] for a complete review).

The insulin-like growth factor-type I (IGF-I) may serve as a biochemical marker in GHD. However, careful consideration must be made to its high variability according to age, sex and body mass index [16]. Confirmed low levels of IGF-I in the setting of a high clinical probability may be diagnostic. But there are patients with GHD who exhibit normal levels of IGF-I, and, again, there may be an overlap between normal and deficient patients, especially with increasing age [18].

Therefore, diagnosis of GHD is not exempt from pitfalls, making it sometimes truly complex. If we adequately focus it, we will be able to establish appropriate replacement treatment. Moreover, the analysis of serum samples for GH and IGF-1 concentrations should be measured by assays which are standardized to the WHO calibration standards and assays which comply with recommendations on assay standardization as outlined by Clemmons [19]. This is important because the cut-off point during a GH stimulation test will depend on the GH assay used and there is a lack of cross-validation of different assays. As for the measurement of IGF-1, differences in assay performance must be taken into account when evaluating and monitoring patients with GH disorders, because agreement among IGF-I assay methods is only moderate to good, as has been recently reported by Mavromati et al. [18]. The authors recommend the use of the same assay for IGF-1 during follow-up.

Do we have a marker to monitor treatment and its response?

In a similar way to the difficulties encountered in the diagnosis of GHD, monitoring the outcome and response to treatment may be equally challenging, mainly because there is no clinical objective parameter which could be unequivocally useful (such as growth in children), and IGF-I levels may be highly variable [2, 18, 20].

In the setting of adult GHD, current guidelines [21] recommend periodic follow-up of (Table 1):

- Anthropometric parameters: weight, body mass index, waist-to-hip ratio, body composition and blood pressure.

Table 1 Listing of the most frequent parameters which are monitored in the follow-up of patients receiving rhGH replacement therapy (adapted from [18])

Anthropometric parameters	- Body weight, body mass index
	- Waist/hip ratio
	- Body composition
	- Systolic and diastolic blood pressure
Analytical parameters	- IGF-I
	- Lipid profile (total cholesterol and LDL/HDL fractions)
	- Fasting plasma glucose, HbA1c
	- Renal and hepatic function
Quality of life	- AGHDA test the most frequently used
Secondary effects	- Edema, headache, arthralgias, compressive neuropathies
	- Magnetic resonance imaging, electrocardiogram, ocular fundus examination

- Analytical data: IGF-I levels, lipid profile, fasting serum glucose, HbA1c, kidney and liver function tests.
- Quality of life: for example, using the AGHDA test.
- Monitoring for adverse outcomes: edema, headache, arthralgias, and compressive neuropathies, amongst others
- Magnetic resonance imaging, ocular fundus and electrocardiogram.

As we can see, body composition and IGF-I levels are the main outcomes that will be monitored, in line with the belief that these parameters would better reflect the actual individual's GH status and would be relatively accessible in routine clinical practice.

Regarding IGF-I, its response to GH administration essentially reflects the hepatic effect of GH, as more than 70% of the circulating IGF-I is produced in the liver [22]. On the other hand, the overall effects of GH are dependent both on GH and IGF-I, and it is likely that many of the anabolic and metabolic effects of GH are primarily mediated through IGF-I [23]. Accordingly, measuring IGF-I levels would presumably serve as a surrogate marker of GH status. However, IGF-I reference levels may be highly variable between individuals, in a same individual, and due to intrinsic technical difficulties in laboratory methods. Moreover, the relationship between serum IGF-I response during GH treatment and other treatment effects such as metabolic endpoints and body composition is not always as straightforward [2, 24]. This hampers the utility of IGF-I as a perfect surrogate marker for other efficacy variables or as a reflection of the effects of GH in all tissues. But in the absence of a generally accepted gold standard, and due to the inherent difficulties in assessing which marker most accurately reflects the individual's GH status, IGF-I levels will still remain valuable and convenient to detect under and over-replacements with GH treatment. In fact, in a study that evaluated the relationship between the administered GH dose and the achieved serum levels of three GH-dependent serum markers, IGF-I, IGF-binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS), IGF-I was the one that better reflected GH activity in various tissues [25].

Evaluation of the outcome of other parameters are also troublesome; for instance, potential changes in bone mineral density require a latency period, whilst quality of life may not change significantly if it was previously not affected. Thus, other simple measures to monitor GH dose titration have been suggested, such as changes in extracellular water, measured using a combination of bioelectrical impedance analysis and arm muscle area [26]. GH seems to increase extracellular water through an anti-natriuretic action in a consistent way during GH treatment, so it has been suggested that this may be a more useful endpoint with which to monitor GH replacement than other aspects of body composition [2, 26].

There have been attempts to identify other potential serum biomarkers, which could aid in the monitoring of GH treatment, and that overcome the limitations of IGF-I. For instance, in a small study in GHD patients that analyzed serum proteomic changes using two-dimensional gel electrophoresis and mass spectrometry, the levels of five isoforms of haptoglobin (which decreased in samples after GH treatment) and one isoform of apolipoprotein A-I (which increased after GH) were associated to the well-known changes in body composition after GH substitution, independently of serum IGF-I levels [27]. These proteins may provide a novel alternative to traditional markers of GH status in GHD patients receiving rhGH treatment, but further studies to evaluate their potential utility in clinical practice deem relevant.

Does GH replacement treatment improve or even avoid the consequences of the deficiency? Is it efficacious?

There is a general consensus that many of the metabolic and psychological abnormalities associated with GHD can be reversed with GH replacement. Particular interest has been directed towards body composition, bone mineral density, cardiovascular outcomes, quality of life and mortality (Fig. 1). Most of improvements are seen during the first year of treatment and are sustained for long period of time (more than 10 years).

Body composition

Current guidelines recommend with moderate quality evidence that GH therapy of GHD adults offers significant clinical benefits in body composition and exercise capacity [4]. This arises from the fact that improvements in body composition have been consistently documented across multiple studies in adult GHD patients receiving GH replacement therapy [5].

Specifically, GH administration promotes lipolysis in total body fat [5, 28], but preferentially, and conveniently, in visceral fat [24, 29, 30], as it has been observed in several studies using computed tomography [31–33]. Besides, the effect may be significant as soon as 6 months after initiation of treatment, and may be maintained for as long as therapy is continued. At the same time, although to a lesser degree than the change observed in fat mass, there is a significant increase in muscle mass in response to GH treatment [32, 34].

If we critically evaluate the outcomes of body composition after GH replacement treatment and deepen in the

findings of published studies, it is worth mentioning that there are subtle differences in GH efficacy regarding sex. For instance, in a randomized, double-blind, placebo-controlled study of 115 patients with pronounced GHD who received rhGH revealed that changes in lean body mass were significantly greater in males than in females, and a similar trend was seen in fat mass [35]. Moreover, and in order to avoid the potential influence of estrogen replacement therapy in the attenuation of the response to GH in women, a study which included postmenopausal estrogen-deficient women in their cohort found significant differences in visceral adipose tissue reduction in men vs. women (18 vs. 5%), and a slight but significantly more pronounced increase in thigh muscle mass in men than in women [33]. The authors suggested that there may be a potential synergic effect of endogenous testosterone in GH action as the underlying mechanism involved in the different response observed between both genders.

Another interesting matter related to the observed changes in body composition is its clinical effects; for instance, the concern of whether or not these modifications (especially increased muscle mass) are relevant for exercise capacity and/or muscle strength. In this regard, in some, but not all, short-term and long-term studies, exercise capacity and physical performance have been improved by GH therapy, with parameters such as maximal oxygen consumption and maximum work capacity being significantly increased [36–38]. Also, in a thorough metaanalysis of 11 randomized, double blind, placebo-controlled, of either parallel or crossover design studies, involving a total of 268 patients, GH replacement was associated with significant improvement with all studies combined, for maximal power output, and maximal oxygen uptake, with no association between age or GH dose on the degree of improvement [39]. However, these positive results were not exempt from several pitfalls that may limit their interpretation. In fact, the authors themselves acknowledge that, in some studies, the magnitude of the effect that was to be evaluated could not be adequately quantified; the interpretation could be misleading because of the low potency of some of the original reports; heterogeneity between individual data; limited exercise-related parameters analyzed; and GH doses which could be considered in a rather high range [39]. In addition, further studies using lower GH doses (0.64 mg/day) than the ones reported in the above-mentioned metaanalysis [40], for example, were not able to prove an effect on the primary endpoints of exercise duration, maximum oxygen consumption and left ventricular ejection fraction at rest and with exercise, and did not change echocardiographic parameters in GHD adults with normal baseline cardiac function.

Regarding muscle strength, some, but not all, studies have shown increases in isometric or isokinetic strength [31, 32, 39, 41, 42], but not all of them were able to prove that this strength returned to normal values comparable to non-GHD patients. Another comprehensive metaanalysis for this issue [43] revealed no significant improvement, neither when all studies were combined, nor when measured individually. Thus, a benefit on muscle strength of GH replacement in GHD patients could not be demonstrated in the short-term, although it is possible that it would truly occur over a longer time-course, as seen in open-label studies.

Bone mineral density

The role of GH in bone biology has been a subject of interest for many decades. In fact, the effects of GH on bone metabolism and bone density seem more complex than and not as straightforward as those observed on body composition [1, 3]. Several in vitro studies have demonstrated a stimulatory effect of GH and IGF-I on osteoblastic and osteoclastic activity, leading to an increased bone formation and turnover [44]. Specifically, GH acts in a biphasic manner in bone: firstly, it increases bone formation while loss of bone can still be identified, but after a transition point, bone formation exceeds bone resorption, and a net gain of bone mass takes place. This shift occurs approximately after 6 months of GH treatment, and bone gain may be evidenced at 12–18 months.

Animal studies suggest that treatment of GHD affects bone microarchitecture [45], and long-term studies have reported a 4–10% increase in bone mineral density (BMD) in rhGH-treated GHD patients, both in comparison to baseline, and in comparison to healthy controls. This increase was generally more evident in vertebral trabecular bone than in femoral sites [46, 47], in males, and when baseline BMD was lower, although studies with even longer follow-up did not reveal such differences in BMD increments regarding sex [48]. Thus, rhGH replacement therapy seems to increase BMD in the context of augmented markers of bone formation and decreased markers of bone resorption [3, 49]. But its role if osteoporosis is also present may not be enough to compensate and prevent the incidence of fractures [50]. Besides, as in general population, in patients with GHD, the development of low BMD and osteoporosis is multifactorial, so other factors should be considered, as well as GHD, including accidental falls due to poor visual acuity, neurologic disturbances secondary to pituitary interventions, genetic syndromes, concomitant treatments (vitamin D, bisphosphonates, and corticosteroids) and muscle mass loss. Data regarding the potential prevention of bone fractures with rhGH replacement in adult GHD are still insufficient to draw definite conclusions. Also, a potential differential effect between sexes has been reported; in this regard, despite inconsistent definition and validation of outcomes, GH replacement longer than

12–18 months raised BMD and decreased the incidence of fractures in adult-onset GHD men, with no difference in adult-onset GHD women.

Cardiovascular outcomes

When addressing cardiovascular outcomes, we usually consider four main areas of pathophysiology: hypertension, lipid alterations, inflammation, and insulin resistance. The interest in evaluating the outcome of these parameters in the setting of GHD arises particularly from the fact that in acromegaly, with high levels of GH and IGF-I, hypertension and diabetes are frequent [51]. Besides, a significant proportion of GHD-derived mortality is caused by cardiovascular factors.

With a low quality evidence, current guidelines suggest that therapy with rhGH in GHD adults improves several cardiovascular surrogate outcomes, including cholesterol, C-reactive protein levels and visceral fat, but tends to increase insulin resistance [4]. Discontinuing long-term (10 year) GH replacement therapy for 4 months (placebo) caused deterioration of surrogate markers [52]. It is important to note that the potential cardiovascular benefit of GH replacement can be seriously attenuated by cigarette smoking.

Specifically, GH replacement therapy has been shown to improve endothelial function, increase flow-mediated dilatation and reduce arterial stiffness [53–55]. Although some large trials have observed a slight decrease in blood pressure with rhGH treatment in GHD patients [56], in general, there is little reference across the literature explicitly regarding hypertension, even though this is a parameter that is frequently routinely monitored in clinical practice. This suggests that there is probably a very subtle and insignificant effect in this parameter in GHD adults over the course of rhGH replacement treatment.

Regarding lipid metabolism, up to half of adult patients with GHD have been reported to exhibit an aberrant and pro-atherosclerotic lipid profile, with increased total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and elevated apolipoprotein B-100 [57]. However, a much lower incidence of hyperlipidemia in subjects with isolated GHD was found in comparison to those with multiple endocrine deficiencies receiving conventional hormone replacement [58], suggesting that lipid abnormalities are not exclusively due to isolated GHD, which may have a minor role in hypopituitary-associated dyslipidemia. The specific size and morphology of LDL particles have only been systematically described in this setting in a few studies [59]. Interestingly, treating adult GHD patients with rhGH proved to increase HDL-cholesterol and decrease LDL-cholesterol, suggesting that the effect of GH replacement on lipoprotein composition and kinetics is more relevant. However, this finding was not consistently reported in all published studies [28, 34, 56, 57, 60–62]. The effect for triglyceride levels, on its part, seems to be neutral [56]. Reasons for the discrepancies observed between studies may include the duration of treatment, the achieved balance between GH-induced stimulation of lipolysis and the improvement in insulin sensitivity, changes in body mass index and visceral fat, and the absence of a specific control over concomitant lipid-lowering medications and/or lifestyle intervention, which could potentially contribute to the overall lipid amelioration during follow-up. In addition, whether rhGH has an additive effect over and above optimum therapy with statins or any other lipid-lowering strategy has not been systematically addressed, and this remains an open question [4].

Inflammatory markers have also been described to be altered in GHD patients. For instance, several studies have observed high levels of C-reactive protein, interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α), which play a role in the increase of cardiovascular risk of GHD, and levels may normalize following rhGH replacement treatment [63, 64]. Similarly, the increased circulating leptin levels observed in GHD patients returned to normal values as IGF-I levels increased with rhGH [65]. In addition, a recent review on the impact of GHD on the cardiovascular and metabolic profile remarked the increased risk of impaired fibrinolysis and thrombosis, thus further increasing cardiovascular morbidity and mortality risk, but the situation seems to normalize after GH replacement [66]. In fact, the plasminogen activator inhibitor-1 (PAI) levels, antithrombin III, C-reactive protein, fibrinogen and pregnancy-associated plasma protein A (PAPP-A) decrease, whilst levels of protein S increase [67–70].

The increased incidence of atheromatous plaques in carotid and femoral arteries, the increased intima-media thickness and the greater carotid and aortic stiffness observed in GHD patients seem to ameliorate following rhGH replacement therapy [66, 71, 72]. At the same time, young adults with GHD have been observed to have a reduced left ventricular (LV) mass, posterior wall, and interventricular septal thickness, LV ejection fraction and an abnormal diastolic filling pattern, using several imaging techniques. But fortunately, a significant improvement in cardiac parameters and morphology has been reported as soon as 6 months after rhGH replacement treatment [66, 73, 74]. However, the effects of replacement therapy with rhGH in GHD patients on cardiac factors have not been fully agreeing. For instance, in a small study of patients with severe GHD to whom cardiac function was evaluated before and after 1 year of rhGH replacement therapy, using cardiac magnetic resonance imaging (CMRI) and measurements of circulating levels of B-type natriuretic peptides

(NT-proBNP), no significant change in LV systolic function or LV mass was evidenced [75]. Thus, the possibility that significant changes in cardiac outcomes correlate with an amelioration in exercise tolerance and energy still deserves further investigation [4].

Besides, there are several issues that should not be disregarded when analyzing the relevance of the above-mentioned results regarding cardiovascular outcomes. Specifically, the well-evidenced improvement in body composition, with patent reductions in visceral and total fat mass, may surely contribute to the overall improvement of the metabolic and cardiovascular profile. Also, intervention on classic and non-classic cardiovascular risk factors has been more intensive in recent years, in comparison to what was routinely done previously (for instance, lifestyle intervention, anti-hypertensive, lipid-lowering or hypoglycemic drugs). Other considerations and critical views to published studies include discrepancies in dose and duration of rhGH treatment, heterogeneity in the type of population studied regarding age, sex, or GHD etiology, other concomitant pituitary deficiencies and replacement therapies (sex hormones, glucocorticoids, and thyroid hormone [61]), the number of patients evaluated, the short or mid-term follow-up, and a relatively low magnitude of the effect. Publication bias, with communication of only positive results, may also be a factor in disguising the results, in addition to IGF-I values which were not always standardized.

Thus, cardiovascular outcomes seem to, in general, improve with GH replacement therapy. But data are still not fully consistent across studies, and may be influenced by other underlying factors.

Quality of life

Assessment of quality of life (QoL) is somehow troublesome, since, in the majority of cases, reports are based on a variety of self-administered questionnaires. In addition, the variety of factors evaluated, including health-related, economic and social factors, may be affected by more than one condition, and not only the specific disease which is being evaluated. In the specific setting of GHD, there have been three main questionnaires which have been validated and are widely used [76]: the Nottingham Health Profile (NHP) [77], the Quality of Life-Assessment for Growth Hormone Deficiency in Adults (QoL-AGHDA) [78, 79] and the Psychological General Well-Being (PGWB) index [80].

GHD patients have been described to be more socially isolated, suffer from tiredness, lack of initiative and concentration, irritability, reduced physical and mental drive, decreased vitality and difficulties in coping with stressful situations, compared to healthy controls [81, 82]. However, there is some controversy in the degree to which QoL is affected in adult patients with GHD. In fact, some untreated patients with GHD reported severe impairment in QoL, whilst others reported it to be normal, particularly in adults with childhood-onset GHD [81]. This may jeopardize the analysis of the potential impact of rhGH replacement therapy on QoL, since demonstrating an improvement would be difficult if baseline impairment is minimal. Thus, selection of patients should be careful and fully described to be able to correctly interpret results.

Treatment with rhGH has been associated to improvements in QoL in GHD adults in several placebo-controlled studies as soon as 3 months after initiation of rhGH replacement therapy [4, 83], and there have been subsequent reports of decrease in healthcare consumption in parallel to these QoL improvements [84]. Moreover, further longer-term studies have also reported improvements after 10 years of rhGH treatment when assessed with two specific questionnaires [85], but others did not achieve a demonstrably different psychological benefit to those patients deciding to discontinue replacement [86]. This is worth remarking, given the chronic and long-term nature of GHD. On the contrary, there are several studies that have observed more limited improvements, or even reported them to be absent, especially if baseline QoL was not affected, and with no influence according to sex [6, 76, 87–90].

Several issues should be critically considered when interpreting studies on QoL. For instance, other concomitant pituitary deficiencies, as well as adverse effects derived from prior pituitary interventions or the pituitary disease itself, may be also involved in patients' impaired QoL. The potential influence of the GH dose was interestingly addressed in a study which reported that an extra dose of GH did not further improve the clinical benefit in QoL, but did induce biochemical overtreatment in about twice as many patients [1].

Therefore, not always can we ascribe the impairment in QoL to GHD exclusively, nor will we be able to report a significant and evident improvement following GH treatment, and the beneficial effects of GH on well-being in adults with GH deficiency should not be used to determine dosing.

Mortality

A large number of epidemiological studies have observed an increased all-cause mortality in hypopituitary patients, when compared to age-matched and sex-matched controls, with the highest mortality among younger patients, women and patients with diabetes insipidus, as it was remarked at the beginning of this review [7]. And there are also studies that have reported reductions in mortality in hypopituitary patients who received optimal hormonal replacement, including rhGH treatment, although these mortality rates still remained higher than in the general population [8].

However, the existing time-lapse between the cohorts of patients compared may entail subtle differences in the management of their comorbidities, including diabetes, dyslipidemia or hypertension, which may distort the interpretation of results. Besides, most of the data available arises from post-marketing surveillance or retrospective studies, which by their nature are not ideal for assessing the impact of GH on mortality, due to their inherent bias, as each patient is deliberately assigned treatment with GH. In fact, randomized placebo-controlled trials assessing the effect of GH therapy on mortality in adult-onset GHD are still lacking, probably due to the duration of follow-up and the number of patients required to adequately power such a study.

Therefore, we are still unsure of whether or not rhGH replacement therapy is truly efficient in reducing all-cause and cardiovascular or cerebrovascular mortality. As a matter of fact, current guidelines only suggest, and with a very low quality of evidence, that GH has not yet been shown to improve mortality [4, 21, 91].

Is treatment with GH safe?

Treatment with recombinant human GH is one of the most enviable regarding its track record of safety [91–93]. In fact, pharmaceutical company-sponsored post-marketing surveillance studies, involving approximately 200,000 patients and more than 500,000 patient-years, provide a great deal of valuable information [94]. However, the methodological limitations of these studies, including that they are open-label, they entail inherent weaknesses in patient cohort surveillance because they depend on physician reports and physician evaluation of whether such events are "GH-related", they may have evaluated changing GH doses and/or recipient characteristics over the course of the study, they are time-limited, they sometimes lack a control group of any kind, they may fail to identify adverse events that only become evident after treatment, and that they are under the control of its sponsoring company, may jeopardize a fully comprehensive and reliable drawing of conclusions.

In any case, patients' fully detailed medical history should be collected before considering rhGH replacement therapy. For instance, besides age progression and obesity, which are risk factors affecting type 2 diabetes mellitus, family history of diabetes is also essential. In fact, it has been shown that diabetes prevalence is strongly influenced by the presence of familial diabetes (19.9 vs. 5.8%). The same is true for cancer, so a complete family history of malignancy should be provided.

Tolerance to GH and development of adverse events

One of the largest and most comprehensive studies regarding GH safety is the Genentech National Cooperative Growth Study (NCGS). Results from more than twenty years of follow-up in almost 55,000 GHD children, even after GH discontinuation, concluded that GH treatment entailed a favorable overall safety profile, although specific populations could be at risk for adverse effects [95]. As it was commented in an interesting editorial [96], these findings pointed out some particularities of the adverse effects observed during the follow-up of children receiving rhGH, including the fact that some of the underlying mechanisms remained unknown [95, 97].

However, the French Sante Adulte GH Enfant (SAGHE), as part of a European consortium entitled SAGhE (Safety and Appropriateness of GH Treatments in Europe), which included around 7000 children with idiopathic GHD, idiopathic short stature and short stature children born small for gestational age, evaluated long-term mortality with opposite findings, with an all-cause standardized mortality ratio of 1.33, with increased mortality due to diseases of the circulatory system, no increased all-type cancer-related mortality, and the majority under the category of "idiopathic," i.e., no cause of death was stated on the death certificate or the investigators were unable to determine the cause of death [97]. Thus, further studies were warranted in order to provide full evidence regarding overall safety of GH.

The majority of the side effects of rhGH replacement therapy seem to be related to fluid retention, with peripheral edema, arthralgias, carpal tunnel syndrome, paresthesias and worsening of glucose tolerance. These hormonal side effects are usually more frequent in obese and older patients, and usually respond to dose reduction. Idiopathic intracranial hypertension (formerly known as pseudotumor cerebrii) has been linked to rhGH treatment in children, but rarely in adults [98].

A prospective observational study in the setting of US clinical practices evaluated the occurrence of adverse events in 1988 GH-treated patients and compared them to 442 GHD untreated patients, as part of the US Hypopituitary Control and Complications Study (HypoCCS) [99]. There were no significant differences in rates of death, cancer, intracranial tumor growth or recurrence, diabetes, or cardiovascular events between both groups, and the standardized mortality ratio was not increased in either group. Differential unexpected adverse events included insomnia, dyspnea, anxiety, sleep apnea, and decreased libido, all below 6.4%. It is worth remarking that some of these adverse effects were related to baseline risk factors, such as obesity and cardiopulmonary disease, higher rhGH dose, or concomitant GH side effects. However, duration of mean follow-up was limited to 2.3 years, which may be

considered insufficient for evaluating safety and not be conclusive for these long-term events. In any case, once again, the importance of patient selection and GH dose titration become essential.

Is there a risk for development of neoplasias?

There has been a theoretical concern that GH therapy and subsequent increased levels of IGF-I could lead to the development or regrowth of malignancies or pituitary tumor regrowth/recurrence [93, 100–102]. However, this increased risk has not been consistently observed in several epidemiological studies, since the presence of confounding factors, including the underlying disease, prior radiotherapy, or dosage of GH treatment, could not be adequately ruled out, and no increase in the recurrence rates of either intracranial or extracranial tumors has been demonstrated in adults with GHD receiving rhGH treatment [103–106]. But, once again, most of the long-term safety data comes from open-label observational studies, with its inherent limitations. So, although most studies did not evidence an increased cancer risk in patients treated with GH, and it can be assumed that, overall, there is no clear effect of rhGH replacement on tumor regrowth or recurrence in adult patients with GHD, the fact that the theoretical association has been shown, determines that rhGH treatment is contraindicated in the setting of active neoplasia [4, 91, 107, 108].

Effects on glucose homeostasis

Effects on glucose tolerance and its potential worsening have been a matter of great concern since the use of rhGH replacement therapy became available. In this regard, in a small study in 11 patients who received low doses of GH and were evaluated with dynamic testing, [109], glucose tolerance and insulin sensitivity significantly deteriorated, and an inappropriate beta-cell response was evidenced, forecasting the potential precipitation of diabetes in susceptible patients treated with rhGH, despite the amelioration of body composition. In a larger double-blind, randomized, placebo-controlled trial [30], rhGH therapy was associated to a worsening of glucose tolerance, which progressed to impaired glucose tolerance in 13% and to diabetes in 4% of patients; and these rates were significantly higher than those who received placebo.

Further studies were performed in the clinical setting, based on the international HypoCCS surveillance database [110]. Fasting plasma glucose values were only mildly and transiently elevated, but attention was brought to the need of monitoring glucose homeostasis in subjects receiving rhGH therapy. In addition, in another study from the same database, an overall incidence of diabetes of 9.7% (14.1% in the United States and 7.0% in Europe) was reported. Adjustment for age, gender and body mass index showed no evidence for increased diabetes incidence in rhGH-treated adult hypopituitary patients, but those more prone to develop diabetes exhibited a higher than normal prevalence of obesity. Interestingly, rhGH dose was not correlated with DM incidence [111].

Another subsequent, larger, long-term observational study [112] selected from the KIMS (Pfizer International Metabolic Database) found that, after a follow-up of 3.9 years, 10.2% of patients developed diabetes after a median of 1.7 (0.02–10.3) years of rhGH treatment, with a reported incidence of 2.6 per 100 patient-years. These newly-diabetic patients were older, had higher body mass index, waist circumference, triglyceride concentrations, and blood pressure, and had lower HDL-cholesterol concentrations than those who did not develop diabetes. Besides, those individuals who did not develop diabetes, experienced a significant increase in fasting glucose and HbA1c levels. Interestingly, and as it had been suggested in previous studies, there was no significant association with the dose of GH administered or the levels of IGF-I achieved.

Therefore, it seems that a greater incidence of diabetes does exist in the setting of GH replacement therapy, and this is especially relevant in patients who exhibit other associated risk factors, such as older age, higher body mass index, and personal or family history of glucose intolerance or diabetes. Worsening of glucose homeostasis appears to be more evident during the first year of GH treatment, but then tends to subsequently ameliorate. This may probably be due to the concomitant improvement in body composition, tapering of GH dosages over the course of follow-up, and control of other associated cardiovascular risk factors. Interestingly, glucose effects are apparently not related to GH doses used. In view of these findings, it seems reasonable to have the precaution of monitoring glucose homeostasis in GHD patients receiving rhGH replacement therapy, and to closely follow diabetic patients, in case they need adjustment of hypoglycemic drugs [4].

Other considerations

Should the patient's age be taken into account?

Patient's age is possibly one of the first considerations that should be born in mind when considering rhGH replacement therapy, once the diagnosis of adult GHD has been established. In fact, although the symptoms of GHD are not age-specific, their relative importance differs over the course of life, with a resulting variability in the impact of GHD on patients' wellbeing [113]. Child-onset and transition GHD were not a topic of this review. But in middle age, however, one of the most worrying features of GHD is

the increase in cardiovascular risk, highly related to dyslipidemia and fat-prone body composition. Therapy with rhGH in this age group seems to durably reduce cholesterol levels and ameliorate the lean mass/fat ratio.

Elderly GHD patients, on their part, experience enhanced normal aging symptoms, with impaired QoL, but rhGH replacement therapy in individuals older than 60 years old with age-adjusted low levels of IGF-I and no history of pituitary or hypothalamic disease is not recommended [21]. In fact, in a systematic review of 11 studies evaluating GHD in patients above 60 years old, treatment with rhGH decreased total and LDL-cholesterol levels, but did not alter HDL or triglyceride levels. In addition, body mass index, blood pressure or bone mineral density were not affected, although there was a subtle improvement in waist circumference. Curiously, body composition was not improved in all studies, in contrast to QoL parameters, which did ameliorate consistently. There were no explicit data on elderly GHD patients aged >80 years [114].

For how long should treatment be maintained?

A recent cohort study evaluated the long-term anthropometric and metabolic effects 3 years after discontinuation of rhGH replacement in adult GHD patients, with a subgroup analyzes according to age (< or >60 years) [115]. Reasons for discontinuation included the development of adverse effects, the absence of a subjective clinical benefit, older age, unwillingness to maintain an injectable treatment, lack of compliance and poor tolerance to treatment. Results evidenced that, after 3 years without rhGH therapy, blood pressure, LDL-cholesterol, fasting glucose and lumbar spine bone mineral density did not change significantly. In contrast, fat percentage increased, body mass index decreased only in subjects <60 years, HDL-cholesterol levels increased only in patients <60 years and femoral neck bone mineral density and bone turnover markers decreased in subjects <60 years. The same authors performed a systematic review, which included eight studies with 166 patients and a follow-up of 6–18 months. Their findings revealed that discontinuation of rhGH was associated to increased fat mass and increased LDL-cholesterol in three studies, stable fasting glucose values in two studies, deterioration of QoL in adults under 60 years old in two studies, but not in those >60 years old, and controversial results regarding the outcome of bone mineral density [115]. Thus, rhGH discontinuation does not seem to have a significant negative impact in the metabolic profile of those patients older than 60 years old, whilst results are less evident for those under 60. It is interesting to remark that none of the studies mentioned handling of statins, bisphosphonates, and glucose-lowering medication or excluded patients on these medications. In addition, the reported end points were heterogeneous, did not report on raw data, and differed between studies, precluding a formal meta-analysis.

We can, therefore, suggest, that the patient's age and the expected duration of treatment should be parameters to be taken into account when considering rhGH replacement therapy. However, we still need further studies to be able to determine the time and optimal strategies for rhGH withdrawal in aging GHD patients. Dyslipidemia and hypertension should probably not be the sole issue to consider rhGH replacement therapy, since there are alternative well-documented and with high quality treatment approaches. However, QoL, patients' preferences, efficacy/safety issues and associated costs should be performed in future long-term studies. In any case, continuous and long-term monitoring and reevaluation of patients deem necessary to correctly manage adults with GHD.

Is treatment easy to administer, or, at least, bearable?

Traditional treatment has entailed the use of daily subcutaneous injections of rhGH, In this regard, different rhGH formulations and presentations are available across countries, promoted by several brands and trademarks, with considerable improvements in the easiness of management and conservation of devices in recent years.

However, this regime does not fully resemble physiologic GH secretion, nor it proves completely practical and convenient for patients, thus potentially entailing efficacy and compliance issues. As a result, longer-acting rhGH formulations and analogs have been developed in recent years, including encapsulation of GH into biodegradable polylactic acid-co-glycolic acid (PLGA) microspheres [116, 117], a GH-loaded hyaluronate microparticle (LB03002) [118, 119], which first became available in Korea, and pegylation, i.e., the attachment of polyethylene glycol, PEG (PHA-794428), which was discontinued due to safety concerns related to local injection-site lipoatrophy [120]. In addition to these sustained-release preparations and prolonged half-life derivatives, new injectors that cause less pain, and other noninvasive delivery methods such as intranasal, pulmonary and transdermal deliveries have been subsequently developed and are under evaluation [121].

In any case, and regardless of the fact that treatment is, for the moment, injectable, patients do not seem to be significantly troubled, and, in general, do comply with the proposed regime [4, 81].

Is treatment economically sustainable?

Cost-effectiveness studies of the use of rhGH in adults with GHD are scarce; in fact, the majority of the studies in the setting of GHD are limited to the use of rhGH in children [122]. A Swedish study [123] performed a Markov-type

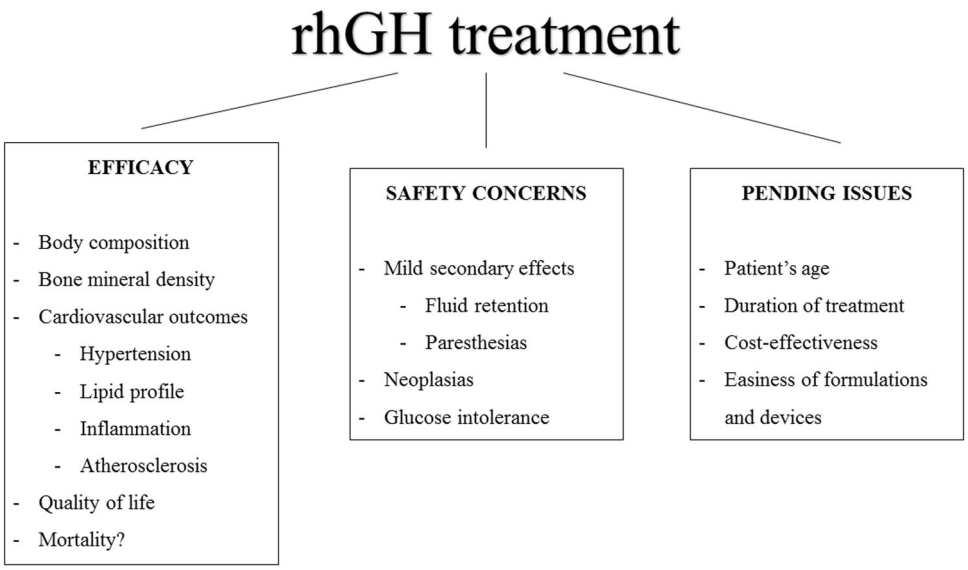

Fig. 2 Summary of the main considerations to be taken into account regarding rhGH treatment in adults with GH deficiency (GHD)

cost-utility simulation model and found a moderate incremental cost per quality-adjusted life year (QALY) gained, including both direct and indirect costs for rhGH-treated vs. untreated patients, suggesting that rhGH treatment is cost-effective. It is true that with escalating health-care costs, the chronicity of certain diseases such as GHD, aging population and the availability of new pharmaceutical drug developments, the need for economic evaluations deems necessary to be able to guide clinicians in decision-making and patient approach. However, whatever the case may be, we should always still try to aim for the maximum benefit of patients and avoiding of harm.

Final comments, summary and conclusions

Several studies have acknowledged the potential consequences of GHD, with a significantly increased morbidity and mortality (Fig. 2). Although the diagnosis of GHD is not easy and straightforward in the majority of cases, a thorough attempt should be made to adequately assess those individuals who are at a higher risk of exhibiting GHD. In the same way, monitoring of GH replacement therapy becomes difficult, given the absence of an unequivocal and objective parameter. Thus, calling upon a mix of clinical and analytical variables, including body composition, bone mineral density, cardiovascular outcomes, quality of life, and IGF-I, will presumably guide clinicians over the duration of follow-up. In this regard, for instance, some authors have proposed a clinical response score to rhGH therapy in adult GHD, based on changes in total cholesterol, waist circumference and QoL-AGHDA measurements [124], which turned out to seem helpful. Patients' baseline characteristics influence their potential response to rhGH treatment, and may, as well, predict the development of adverse events. Continuous monitoring and reevaluation of the need of rhGH deems relevant, especially given the lack of clear evidence of the effects of discontinuing rhGH therapy in elderly patients.

We could say that, overall, the main pros of rhGH treatment in adult GHD patients include the fact that the efficacy of treatment is well described, there is an abundance of safety data, and the consequences are well described. However, rhGH treatment is expensive, entails daily injections, and we are still unaware of further potential consequences of adult GHD, so more safety data is still needed, because many studies lack an adequate control population. In addition, compliance and adherence to treatment is an issue with daily rhGH injections, which should be taken into account when interpreting study outcomes.

Future long-term studies on mortality and cost-effectiveness and the direct comparisons between GH-treated vs. non-GH-treated groups will help elucidate pending issues regarding the effectiveness of rhGH in adult GHD.

Compliance with ethical standards

Conflict of interest A.R.L. has received lecture fees from Ipsen, Pfizer and Novartis. M.M. has received lecture fees, advisor fees and research grants from Pfizer and lecture fees from Novartis and Ipsen. The remaining author declares that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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