REVIEW

GH replacement therapy in elderly GH-deficient patients: a systematic review

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Abstract

Context: Recombinant human GH (rhGH) is prescribed for the treatment of adults with GH deficiency (GHD). However, conflicting data are available on the efficacy of rhGH treatment in elderly GHD patients.

Objective: To assess the efficacy of rhGH treatment in elderly GHD subjects.

Methods: We searched the available literature in PubMed, Cochrane Library, Web of Science and EMBASE.

Study selection: Studies on GHD patients, aged >60 years, treated with rhGH were eligible for inclusion. Data extraction was performed by two reviewers independently.

Results: We found 11 eligible studies with a total of 534 patients. Only two studies had prospective, randomized, placebo-controlled study designs of rhGH treatment with a duration of 6 ($n=15$) and 12 months ($n=62$), respectively. Treatment with rhGH decreased total and low density lipoprotein (LDL) cholesterol levels by 4–8 and 11–16%, respectively, but did not alter high density lipoprotein or triglyceride levels. RhGH did not affect body mass index, but decreased waist circumference (by ~ 3 cm) and waist/hip ratio. RhGH did not consistently affect blood pressure or bone mineral density. RhGH increased lean body mass by 2–5% and decreased total fat mass by 7–10% in four studies, but did not affect body composition in two other studies. RhGH consistently improved quality of life (QoL) parameters reflected in AGHDA-scores. There were no explicit data on elderly GHD patients aged >80 years.

Conclusion: RhGH replacement in elderly subjects with GHD decreases LDL cholesterol levels and improves QoL, but the effects on other parameters are not unequivocal. There were no data on the efficacy and safety of rhGH treatment in octogenarians with GHD.

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Introduction

In healthy adults, GH secretion declines with increasing age (1, 2). Some of the clinical features of normal aging resemble the manifestations of pathological GH deficiency (GHD). These features include changes in body composition (BC), such as increased total fat mass, decreased lean body mass (LBM) and decreased bone mass, as well as a higher prevalence of cardiovascular risk factors and diminished cardiac function (3).

Consequently, a number of studies have examined the effect of recombinant human GH (rhGH) on various clinical parameters in otherwise healthy elderly subjects (4) as well as in elderly patients with GHD. Rudman *et al.* (5) were the first to report that 6 months of rhGH treatment in healthy elderly men reduced adiposity and increased muscle mass and bone mineral density (BMD). Other studies observed similar beneficial effects, suggesting a potential role for rhGH as anti-aging therapy (6–8). A recent systematic review and meta-analysis of randomized controlled trials observed that rhGH treatment decreased overall fat mass decreased by

~ 2.1 kg and increased overall LBM increased by ~ 2.1 kg (CI, 1.3–2.9) ($P<0.001$), without any effect on weight. However, rhGH was associated with increased rates of adverse effects (4). Moreover, in healthy elderly subjects, higher physiological insulin-like growth factor 1 (IGF1) concentrations are associated with increased mortality (9).

Several studies assessed the clinical benefits of rhGH therapy in elderly GHD patients. Some studies in elderly patients with GHD documented that, rhGH improved quality of life (QoL) (10, 11), BC (12–14) and lipoprotein profiles (11, 15, 16), although another study showed no effects (17). A consensus statement on the treatment of GHD adults states that ‘the age-related decline in the GH–IGF1 status does not warrant rhGH supplementation, but patients with proven GHD should be treated’. These guidelines indicate that the dose of rhGH should be adjusted with advancing age, because of the normal age-related decline in GH secretion (18). Apparently, there is no clear age limitation in treating elderly GHD adults with rhGH.

The aim of the present study was to critically assess the available literature in order to evaluate the available evidence for treatments of elderly patients with GHD. Therefore, we performed a structured review of the available literature on this subject.

Subjects and methods

Search strategy

We performed a systematic search in the following databases: PubMed, EMBASE, Web of Science, Cochrane Library, CINAHL database and Academic Search Premier. The search strategy included three main issues: GHD, age >60 years and GH replacement therapy. We used all relevant keyword variations, including free text words. This resulted in the following search string: (((("Growth hormone deficiency"[ti] OR "Growth Hormone/deficiency"[Majr] OR "GH deficiency"[ti] OR "Growth hormone deficient"[ti] OR "GH deficient"[ti] OR GHD[ti]) AND ("aged"[Mesh] OR elderly[tw] OR oldest old OR Nonagenarians OR Nonagenarian OR septuagenarian OR septuagenarians OR Octogenarians OR Octogenarian OR Centenarians OR Centenarian)) OR (("Growth hormone deficiency"[ti] OR "Growth Hormone/deficiency"[Majr] OR "GH deficiency"[ti] OR "Growth hormone deficient"[ti] OR "GH deficient"[ti] OR GHD[ti] OR "Growth hormone deficiency" OR "growth hormone deficient" OR "gh deficiency" OR "gh deficient") AND ("Growth Hormone/administration and dosage"[Mesh] OR "GH/therapeutic use"[Mesh] OR "Growth Hormone/therapy"[Mesh] OR ((growth hormone OR growth hormones OR Somatotropin OR Somatotropins) AND (therapy OR therapeutic OR replacement))) AND ("aged"[mesh] OR elderly[tw] OR oldest old OR Nonagenarians OR Nonagenarian OR septuagenarian OR septuagenarians OR Octogenarians OR Octogenarian OR Centenarians OR Centenarian))) AND (English[lang]. Furthermore, the references of relevant articles were checked for additional articles. The following exclusion criteria were used: age <60 year, non-GHD subjects and no rhGH therapy.

Data review

The following data were extracted from each study: i) age, gender and number of patients, ii) the endocrine tests used to diagnose GHD, iii) criteria used to define GHD, iv) duration of treatment and treatment dose and v) the effect of GH on individual outcome parameters.

Results

The initial search resulted in a total of 577 articles (527 in PubMed, 3 in Cochrane Library, 15 in Web of Science and 26 in EMBASE, 0 CINAHL database and

6 Academic Search Premier). Of these 577 articles, 534 were unique without duplications. We excluded 403 papers based on title and abstract (studies on GHD without specific focus on rhGH replacement therapy and/or age <60 years ($n=326$) and reviews ($n=77$)). In 89 additional papers, which included patients with an age >60 years, the individual data of the patients could not be extracted. Two additional papers were not available for evaluation.

Therefore, a total of 40 potentially relevant manuscripts were retrieved for full assessment, of which 26 studies were excluded from further analysis because those studies did not meet one or more of the eligibility criteria (age <60 years, no rhGH therapy and healthy elderly).

Ultimately, the search strategy resulted in a total of 14 manuscripts meeting our inclusion criteria. However, only eight different cohorts of patients were described in these 14 studies, because several studies described data from the same patient cohort. The studies by Götherström *et al.* (12, 19) described the same patient cohort ($n=24$) after 5 and 10 years of rhGH treatment. The studies by Elzgyri *et al.* (16) and Fernholm *et al.* (13) ($n=31$) as well as Gill *et al.* (14) and Toogood *et al.* (20) ($n=12$) also described the same patient cohort. Therefore, the data of these studies are described in combination. (12–14, 16, 19, 20) The studies reported from the KIMS database included different numbers of patients in each publication ($n=64$, $n=125$, $n=135$, $n=64$). Although it is likely that similar patients have been included, the different numbers of subjects preclude combination of the data of these separate studies (10, 11, 15, 21).

Consequently, a total of 11 studies were included in the present review, comprising 534 patients (Fig. 1).

Study designs

Two studies ($n=65$) had a prospective placebo-controlled, randomized design assessing the effects of rhGH treatment during 6 ($n=15$) and 12 ($n=62$) months, respectively, in elderly GHD patients (16, 17). The study by Elzgyri *et al.* (16), that evaluated the effects of rhGH versus placebo for 6 months, was continued for another 12 months using a non-randomized prospective study design.

The other nine studies had a non-randomized prospective study design, in which the basal data prior to rhGH treatment were used to assess the effects of rhGH ($n=469$). Four of these studies ($n=388$) used patients derived from the KIMS database (10, 11, 15, 21).

In this review, we only included studies on patients above the age of 60 years. Two studies did not specify the age of the patient, but only indicate that all patients are >60 years (10, 11). One study assessed patients between the age 60 and 70 years (22), and in three

Figure 1 Summary of study assessment and exclusion stages.

studies, the age ranged between 60 and 75 years (12, 21, 23). Five studies included patients > 75 years and only two of these studies included patients with age > 80 years (14–17, 24).

Endocrine evaluation

All 11 studies used stimulation tests for the evaluation of GH reserve (Table 1). Different tests, however, were used, including insulin tolerance test (ITT), combined GHRH plus arginine (GHRH + arginine) test, glucagon stimulation test or stimulation with arginine alone (Table 1). The ITT was used in the total population or in the majority of patients in seven studies (11, 12, 15, 17, 21–23). The study by Koltowska *et al.* (10) did not mention which tests were used to diagnose GHD. However, that study also described patients from the KIMS database, and, therefore, it can be assumed that the ITT was also used in the majority of these patients. The remaining three studies either used GHRH tests (16), arginine tests (14) or combined GHRH + arginine tests (24). All but one study applied the generally used cut-off value for severe GHD of a peak GH < 3 µg/l. In the study by De Marinis *et al.* (24), which used the GHRH + arginine test, severe GHD was defined as a GH peak < 15 µg/l, without corrections for the effects of body mass index (BMI).

Duration and dose of rhGH treatment

The duration of treatment with rhGH ranged from 6 months ($n=15$) to 10 years ($n=24$). Six studies ($n=390$) calculated the GH dose based on bodyweight (11, 12, 15, 16, 21, 24). One of these studies used a predefined dose per kg bodyweight per day (0.0119 mg/kg per day) (12). The other five studies titrated the rhGH dose/kg per week (0.017–0.042 mg/kg per week) (11, 15, 16, 21, 24).

Of the remaining five studies, one study gave three fixed doses of rhGH (0.17, 0.33, and 0.5 mg/day) for 12 weeks. These patients received the highest dose of rhGH, i.e. 0.5 mg/day (14). In the remaining four studies, rhGH was titrated on an individual basis with the aim to reach IGF1 levels within the normal age- and sex-related range or clinical improvements, taking QoL and BC into account. The mean dose of rhGH ranged from 0.11 to 0.37 mg/day (11, 15, 21, 24).

IGF1 levels and s.d. scores

Seven of the 11 studies used age-adjusted IGF1 levels measured in a control population to titrate rhGH dose (11, 12, 14, 16, 21–23). Götherström *et al.* (19) and Franco *et al.* (8) both used the same reference values measured in a group of 392 patients aged between 25 and 64 years, as described by Landin-Wilhelmsen *et al.* (25). Feldt-Rasmussen *et al.* (11) and Monson *et al.* (15, 21) both refer to a study by Drake *et al.* (26). However, that study does not mention the IGF1 reference values, but refers to a dose finding study by Janssen *et al.* (27), in which normative data were based on 54 healthy control subjects aged 20–70 years. The study by Elzgyri *et al.* (16) used reference values derived from the study by Hilding *et al.* (28), in which IGF1 values were measured in a population of 448 healthy controls aged 20–96 years. The remaining two studies measured reference values in an own reference population of 450 (18–80 years) (22) and 124 (60–84 years) (14) healthy controls, respectively.

All studies titrated the rhGH dose with the aim of normalizing IGF1 s.d. scores, i.e. aiming at IGF1 SDS in physiological levels for age and sex (between -2 and $+2$). However, four studies also took the clinical response and BC into account for titration of the rhGH dose. Feldt-Rasmussen *et al.* (11) and Monson *et al.* (15) both took the clinical response into account when titrating rhGH dose, referring to a study by Drake *et al.* (26), in which waist/hip (W/H) measurements and improvement of QoL measured by AGHDA were taken into account for the titration of the dose. The remaining two studies (12, 23) both state that, when adjusting the rhGH dose, the aim is to ‘normalizing IGF1 and BC...’, both referring to a study by Johannsson *et al.* (7), in which individualized doses of rhGH are compared with doses based on body weight. In their study, normalization of BC was of great importance and normal values derived from a study by Bruce *et al.* (29), comprising 376 patients in the age 20–70 years, were used to evaluate patients and adjust rhGH levels.

Effects of rhGH on cardiovascular and metabolic parameters

Nine studies ($n=460$) assessed the effects of rhGH on cardiovascular risk factors (11, 12, 14–17, 21, 23, 24). Five studies ($n=424$) assessed the effects on plasma

Table 1 Studies on rhGH therapy in elderly patients with GHD.

Study	Patients	Definition of GHD	T. dur	Dose (mg/day)	IGF1 SDS	Evaluation	Effect of treatment				
							Metabolic Syndrome				
							Anthro.	Lipids	Bone	BC	QoL/cognition
(12)	n=24 M: 11 F: 13 65 (61–74) y	ITT (n=22) GHRH-pyr (n=1) Low IGF1 (n=2)	10 y	Mean initial dose 0.72 in 5 y ↓ 0.37	After 10 y: ↑ –1.10 (1.08) to 1.17 (1.52)	Physical exam. BC (DEXA) Muscle strength ^a	BW: ↓ Height: ↓ BMI: =	–	–	BF: ↓ LBM: ↑	–
(19)		Peak GH <3 µg/l	5 y	Aim normalizing IGF1 SDS (–2 to +2) and BC							4-comp model: BF, BCM, and ECW: =
(10)	n=64 > 60 y (KIMS) n=286 < 60 y	ITT Arginine GHRH Glucagon	6 y	Mean after 1 y: 0.26–0.40	Baseline: –1.3 (1.19) to –2.1 (1.75) After 1 y: 0.8 (1.4) to 0.5 (1.31) Baseline: bet. 0 and –4	QoL (AGHDA)	–	–	–	–	Both groups: AGHDA: +
(11)	n=125 > 65 y (KIMS) n=2469 < 65 y M: 1249	Peak GH <3 µg/l ITT Arginine GHRH Glucagon	12 mo	Mean 0.2 Titration based on clinical response and IGF1 SDS	After 12 mo: Bet. –2 and +2	Physical exam. Lipids BC (DEXA) QoL (AGHDA)	Both groups: Waist (n=114): ↓ W/H-ratio: ↓ BP: <65 y: DBP ↓ F >65 y: DBP ↓ M Both groups: waist (n=93): ↓ W/H-ratio: ↓ BP(n=123): <65 y: DBP ↓ F >65 y: DBP ↓ M	TC (n=107): ↓ LDL: ↓ HDL: TG: =	–	Both groups: LBM (n=47): ↑ AGHDA (n=98): +	Both groups: AGHDA (n=78): +
(21)	n=135 > 65 y (KIMS) (65–74) M: 83 n=1395 < 65 y	Peak GH <3 µg/l ITT (55%) Arginine (14%) Glucagon (5%) Other (26%)	12 mo	Start dose max 0.042–0.083 mg/kg/wk	Baseline: M: median –1.60 (–3.19 to +0.28) F: median –1.78 (–3.81 to 0.06) After 1 y: bet. –2 and +3	Physical exam. Lipids QoL (AGHDA)	–	–	–	–	Both groups: AGHDA (n=78): +
(15)	n=64 (KIMS) 68 (65–82) y n=863 < 65 y	ITT (44%) Arginine (19%) GHRH (13%) Glucagon (11%)	> 6 mo	Mean: 0.37 Titration based on clinical response and IGF1 SDS	Target: Bet. +1 and +2	6 mo (n=64): BP QoL (AGHDA)	Waist: <65 y ↓ Only F >65 y ↓ BP: >65 y: DBP ↓ M	TC: ↓ LDL: ↓ HDL: TG: =	–	–	Both groups: AGHDA: +
(17)	n=34 M: 22 66 (60–77) y n=16 rGH n=18 placebo	Peak GH <3 µg/l ITT Arginine	12 mo	Mean: 0.16 (0.10–0.30) Titration based on IGF1 SDS	Target: Bet. +1 and +2	12 mo (n=22): Lipids, Bone Fasting glucose, insulin, HbA1c Cognitive function Mood	HbA1c, insulin, fasting glucose: no differences	–	–	–	Cognition: no benefits
(22)	n=24 M: 15 68 (65–75) y	ITT (n=41) GHRH (n=3), Glucagon (n=1)	2 y	Mean: 0.31 (0.03) Normalizing age adjusted IGF1 levels and BC	Target: Bet. 0 and +2	Physical exam. BC (DEXA) Bone (DEXA) Lipids, Glucose metab	Both groups: BW: = Waist: ↓ W/H-ratio: ↓ Transient BP ↓	>65 y: LDL: ↓ TC: ↓	Both groups: Osteocalcin: ↑ Calcium: ↑ PTH: unaffected	Both groups: no differences	–
(23)	n=24 M: 15 37 (27–46) y n=10 M: 5 60–68 y n=22 M: 6 26–57 y	Peak GH <3 µg/l ITT Peak GH <3 µg/l	12 mo	Mean: 0.29 (0.03) Maintaining IGF1 within 2 s.d. of age related ref range	Baseline: Mean –2.72 ± 1.17 After 1 month: Mean –0.38 ± 0.96	Bone	–	–	–	–	Both groups: PTH target-organ sensitivity: ↑ ^b

Table 1 Continued

Study	Patients	Definition of GHD	T. dur	Dose (mg/day)	IGF1 SDS	Evaluation	Effect of treatment			
							Metabolic Syndrome			
							Anthro.	Bone	BC	QoL/cognition
(16)	n=31 M: 25 68 (60–79) y	GHRH (n=29) ITT (n=2)	6 mo rhGH: n=15 Placebo: n=16	1 mo: 0.017 5 mo: 0.033 mg/kg/wk	Baseline: All patients below normal mean for age	BP, heart rate Lipids ECG Exercise tests	6 and 12 mo. No changes on cardiac noninvasive structural and functional parameters	6 mo Both groups: TC: ↓ LDL: ↓ LDL/HDL ratio: ↓		
		Peak GH <3 µg/l	12 mo rhGH: n=28	11 mo 0.033 mg/kg/wk Normal range IGF1 assessed by n=448 healthy subjects (20–96 y)	6 mo: 6.9 to 18.5 nmol/l (10.4–32.8) 12 mo: mean 18.8 ± 1.6	BC (DEXA) Bone	BP: =	12 mo TC: ↓ LDL: ↓ HDL: ↑ BMD: no changes Markers bone formation: ↑	6 and 12 mo: Only in M Placebo: no response GH groups: LBM: ↑ TBF: ↓ No changes	–
(13)										
(24)	n=11 M: 6 60–78 y	GHRH-arg Peak GH <15 µg/l	12 mo	0.06–0.12 IU/kg/wk Keep IGF1 levels in psychological range for age and sex	NR	BMI Waist BC	BMI: = W/H ratio: =	–		
(14)	n=39 M: 19 18–57 y n=12 M: 9 68 (62–85) y	Arginine Peak GH <3 µg/l	9 mo	Acute study: single bolus 0.1 mg/kg/BW Chronic study: 0.17, 0.33, 0.5, each dose 3 mo Relationship age and IGF1 assessed in group n=124 (60–87 y) with specific equations ^c	Baseline: Bet. –2 and 0 0.17 mg/day: normal limits 0.33 mg/day: n=2 > +2 0.50 mg/day: n=6 > +2	BC (DEXA) QoL (AHGDA)			FM: ↓ LBM: ↑	AGHDA: +
(20)						Leptin Insulin BC (DEXA)	Acute study: leptin: ↑ Insulin: ↑ Chronic study: leptin: = Insulin: ↑			

BCM, body cell mass; BF, body fat; ECW, extra cellular water; FM, fat mass; TC, total cholesterol; =, no changes; y, years; mo, months; T. dur, treatment duration; wk, week; Anthro., Anthropometrics; Bet., Between.

^aOutcome evaluation muscle strength: transient ↑ isometric knee flexor strength and ↑ muscle strength reversed age-related decline in muscle strength. Proximal leg muscle responded more markedly than distal arm muscle groups.

^bPTH ↓, nephro cAMP ↑ adjusted calcium ↑, bone turnover markers ↑.

^cRelationship between age and serum IGF1 is expressed by the following equation: serum IGF1 (µg/l) = (–1.9347 3 × age) + 286.14; s.d. = 52.67 µg/l. The age-specific s.d. score was calculated using the following formula: s.d. score = (serum IGF1 – (1.9347 3 age)/52.665).

lipid profiles (11, 15, 16, 21, 23). In general, rhGH treatment decreased total and low density lipoprotein (LDL) cholesterol levels by 4–8% (15, 16, 23) and by 11–16%, respectively, whereas rhGH increased high density lipoprotein (HDL) only by 17% in one other study (16). Treatment with rhGH did not affect triglyceride (TG) levels at all.

Six studies assessed the effects of rhGH on body weight, height, BMI and/or W/H ratios (11, 12, 15, 21, 23, 24). In two studies, rhGH did not affect BMI (12, 24). In three of five studies which reported W/H ratios, there was a significant decrease in waist circumference (3 cm in the study by Franco *et al.* 2006 (23)) and W/H ratios (11, 15, 21, 23). However, the two other studies did not find any effect of rhGH on W/H ratios (15, 24).

Five studies assessed the effects of rhGH on blood pressure (BP) ($n=379$) (11, 15, 16, 21, 23). There were no clear consistent effects of rhGH treatment on BP. Treatment with rhGH did not affect (16), only transiently decreased BP (23), or decreased diastolic BP only (11, 15, 21).

One study used an exercise test to evaluate cardiac function ($n=31$). Treatment with rhGH induced a transient increase in heart rate at rest and exercise. However, rhGH treatment did not affect cardiac structural and functional parameters (16).

Effects of rhGH on bone parameters

The effects of rhGH therapy on bone metabolism were evaluated in three studies ($n=65$). Treatment with rhGH did not affect BMD. One study found that treatment with rhGH increased osteocalcin and calcium levels without any change in PTH levels (23). Another study found that rhGH treatment lowered PTH and urinary cAMP levels, associated with higher adjusted calcium and bone turnover markers, indicating a higher PTH target organ sensitivity (22). The third study observed that treatment with rhGH induced higher markers for bone formation (bone-specific alkaline phosphatase activity, osteocalcin and procollagen I carboxyl-terminal peptide in serum) (13). The effects of rhGH treatment on fracture incidence were not described.

Effects of rhGH on BC

Six studies assessed the effects of rhGH on BC using DEXA scan ($n=138$) (11, 12, 14, 16, 23, 24). Two studies ($n=35$) found no effect of rhGH on BC (23, 24). In contrast, the other four studies ($n=103$) found that 6 months of rhGH treatment induced a significant increase in LBM by 2–5% and a significant decrease in total body fat by 7–10% (12, 14, 16). Moreover, these effects of rhGH on BC were reversed, when rhGH therapy was subsequently stopped ($n=12$) (14). One study used a four-compartment model to assess body

fat, body cell mass and extracellular weight, but these parameters were not affected by rhGH therapy (12, 19).

Effects of rhGH on QoL and cognitive functioning

The effects of rhGH treatment on QoL parameters was assessed using only the AGHDA questionnaire in five studies ($n=400$) (10, 11, 14, 15, 21). The majority of these patients were from the KIMS database ($n=388$). Treatment with rhGH induced significant improvements of AGHDA scores in all studies.

Only one study assessed cognitive functioning ($n=34$) using computerized psychometric test package (Neurobehavioral Examination-System 2). However, compared with placebo, rhGH therapy was not associated with improvement in cognition after 12 months.

Effects of rhGH on muscle strength

One study assessed the effects of 5 and 10 years of rhGH treatment on muscle strength ($n=24$) (12). Treatment with rhGH induced a transient improvement only in knee flexor strength. However, rhGH treatment protected from most of the normal age-related decline in muscle performance and neuromuscular function.

Adverse effects

Six of the 11 studies mention possible adverse effects of rhGH treatment. In two studies, the number of adverse events (AEs) was similar for younger and older patients with GHD (11, 15). However, younger patients appeared to have more AEs related to fluid retention (i.e. headaches, edema and arthralgias), whereas patients >65 years had more AEs related to glucose metabolism, cerebrovascular events and neoplasms (11). One of the two placebo-controlled studies mentioned AEs and found no differences between the placebo and rhGH groups (17).

In the study by Fernholm *et al.* (13), 25% of the patients (8/31) developed side effects, probably due to fluid retention (peripheral edema, joint stiffness and muscle pain). However, these side effects subsided spontaneously or after minor dose reduction. The study using the highest dose found AEs in three of the 12 patients. The AEs subsided when the dose was down titrated (20). One study needed to reduce the dose of rhGH because of symptoms of the carpal tunnel syndrome (22).

Discussion

This systematic literature review assessed the effects of rhGH treatment in elderly GHD patients. The data

indicate unequivocally that rhGH treatment positively affects total and LDL cholesterol levels and QoL parameters. There is controversy on the effects of rhGH substitution on other cardiovascular risk factors, including insulin, HDL cholesterol, BP and BC, whereas rhGH therapy does not improve plasma triglyceride levels. Moreover, treatment with rhGH did not improve BMD in elderly subjects with GHD. Finally, studies on the effects of rhGH treatment in elderly GHD patients on clinically relevant endpoints, e.g. cardiovascular morbidity, fractures and mortality, have not been reported.

There is hardly any information on the treatment of very old GHD patients with rhGH. Although two studies included patients >80 years, data on these patients could not be extracted. Therefore, at present, there is no information with respect to the efficacy and safety of rhGH treatment in GHD octogenarians.

All patients described in the studies included in this systematic review were diagnosed with severe GHD, based on different endocrine stimulation tests. However, because of the decline in GH secretion during aging, it may have affected the cut-off values of the GH stimulation tests. Studies using the ITT have been performed in these patients with various results. A study by Finucane *et al.* (30) show that the ITT is a safe test even in elderly patients. However, other studies do show a lower GH response to ITT in the elderly (31). Nonetheless, the ITT is contraindicated in patients with cardiac ischemia or arrhythmias. There are discrepancies between the studies on the cut-off values of the combined GHRH + arginine test and of the arginine test. In previous studies, age seemed to be of no influence when using these tests (32, 33). However, there is a significantly lower peak GH response in elderly compared with younger patients in the GHRH + arginine test (34). Therefore, the omission to reduce the cut-off values of GH stimulation tests in aging subjects may result in an erroneous diagnosis of GHD in some of these subjects. The extent to which this may have affected the conclusions is uncertain, at present.

During aging, GH secretion decreases, associated with a decline in IGF1 levels. Therefore, age-adjusted IGF1 s.d. scores are necessary to be able to assess the treatment response to rhGH. All studies titrated the rhGH dose with the aim of normalizing IGF1 s.d. scores, i.e. aiming at IGF1 SDS in physiological levels for age and sex (between -2 and +2). However, from the analysis described in the results section, it becomes evident that, in some studies, s.d. scores were higher. In addition, some studies included the response of BC to titrate the rhGH dose. Finally, some studies used IGF1 scores from reference populations with a different age distribution. Therefore, there are methodological differences between the included studies, which may have affected the relation between physiological rhGH replacement and responses in elderly subjects.

In GHD elderly subjects, treatment with rhGH had undisputed positive effects on total and LDL cholesterol

levels, and on QoL (10, 11, 14, 15, 21). Treatment with rhGH decreased total and LDL cholesterol levels by 4–8 and 11–18%, respectively. However, the translation of the consistent benefits of rhGH on LDL cholesterol in terms of clinical outcomes is difficult to assess. For instance, it is uncertain whether the beneficial effects induced by rhGH on LDL cholesterol levels will ultimately translate into decreased cardiovascular morbidity and mortality. The effects of changes in this cardiovascular risk factor are not as evident as in younger patients. For instance, in the PROSPER trial, which assessed the effects of primary intervention with pravastatin in elderly subjects with a history of, or risk factors for, vascular disease, baseline LDL cholesterol showed no relation to risk of the primary cardiovascular endpoint in the placebo group, nor did on-treatment LDL cholesterol in the pravastatin group (35).

RhGH decreased W/H ratio in three of the five studies that report this parameter, but this was not confirmed in two other studies. RhGH increased LBM by 2–5% and decreased fat mass by 7–10% (12, 14, 16) in four studies ($n=192$) (11, 12, 14, 16), but this was not confirmed in two other studies ($n=35$) (23, 24). One study documented that these positive effects of rhGH on BC were reversed when rhGH therapy was subsequently stopped, even after only 3 months ($n=12$) (14). Therefore, there are undeniable effects of rhGH substitution in elderly subjects with GHD for some, but not all, parameters.

Several animal models of GHD show prolonged, rather than decreased, longevity. Mice with mutations that cause GHD or GH resistance live longer than their genetically normal siblings (9, 36–39). In addition, adult body size, which can be considered a biological outcome marker of GH actions, was negatively correlated with longevity in other species, including rats (40), horses (41) and domestic dogs (42, 43). Therefore, from an evolutionary perspective, the natural decrease of GH and IGF1 levels during normal aging may even be beneficial. Epidemiological studies in humans, however, documented an association between both decreased and increased IGF1 levels and increased mortality, indicating that the optimal relation between IGF1 and rhGH dose may not be simple (9, 44). Accordingly, it is presently not straightforward that all elderly subjects with GHD should be treated unconditionally.

In conclusion, only a small number of randomized placebo controlled trials have assessed the beneficial effects of rhGH therapy in the elderly. These studies show relatively limited effects. Therefore, the question remains whether the treatment with rhGH is clinically relevant in elderly, and especially very old, patients with GHD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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