

## REVIEW

## THERAPY OF ENDOCRINE DISEASE

# Long-term effects of recombinant human GH replacement in adults with GH deficiency: a systematic review

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## Abstract

**Background:** The beneficial effects of recombinant human GH (rhGH) therapy in GH deficient (GHD) adults are well-established in the short term. However, data documenting the effects during prolonged follow-up are relatively scarce.

**Objective:** To evaluate the reported effects of rhGH replacement ( $\geq 5$  years) in GHD adults on biochemical and anthropometric parameters, quality of life (QoL), bone metabolism, muscle strength, serious adverse events and mortality.

**Methods:** We conducted a systematic literature search. Quality assessment of retrieved papers was performed using a quality assessment based on the modified STROBE statement.

**Results:** We included 23 prospective studies with a rhGH treatment duration ranging from 5 to 15 years. Overall, beneficial effects were reported on QoL, body composition, lipid profile, carotid intima media thickness and bone mineral density. In contrast, the prevalence of the metabolic syndrome, glucose levels, BMI and muscle strength were not, or negatively, influenced. Most of the studies were uncontrolled, lacked the presence of a control group (of non-treated GHD patients), and reported no data on lipid-lowering and anti-diabetic medication. Overall mortality was not increased.

**Conclusion:** rhGH treatment in adult GHD patients is well-tolerated and positively affects QoL in the long term. However, the metabolic and cardiovascular effects during long-term treatment are variable. The low numbers of long-term studies and studied patients and lack of control data hamper definite statements on the efficacy of prolonged treatment. Therefore continuous monitoring of the effects of rhGH replacement to enable an adequate risk-benefit analysis that may justify prolonged, potentially life-long, treatment is advisable.

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## Introduction

GH deficiency (GHD) in adults has been associated with an adverse metabolic profile and increased cardiovascular mortality by inducing abdominal obesity, hypercholesterolaemia and hypertriglyceridaemia (1, 2). Consistent beneficial effects of treatment with recombinant human GH (rhGH) were reported on body composition and lipid profile, resulting in reduction of fat mass combined with an increase in lean body mass (LBM) and a reduction in total cholesterol (TC) levels (3). In addition, favourable effects were reported on bone turnover, bone mineral density (BMD), muscle strength, cognitive function and quality of life (QoL) (3, 4, 5). Most of these effects have been documented in short-term studies, sometimes placebo-controlled, with a follow-up duration ranging from 6 to 18 months.

The beneficial effects of rhGH therapy have been reported to be sustained for at least 5 years of treatment; however, data with a longer follow-up duration are scarce. With respect to cardiovascular disease, a direct improvement of several cardiovascular risk factors was noted within the first treatment year, which was reported to be sustained during prolonged rhGH treatment (6, 7). In a small study, sustained improvement of lipid spectrum and diastolic blood pressure (DBP) was reported over 7 and 10 years, suggesting ongoing beneficial effects even beyond 5 years (6, 7). However, it is presently unknown whether rhGH therapy has favourable effects on the incidence of cardiovascular events, including cardiovascular death. With respect to bone, rhGH replacement therapy increases bone remodeling, indicated by an increase in biochemical markers of both bone formation and

resorption. This results in an initial decline in BMD, followed by a significant increase in BMD, reaching a plateau phase after 5–7 years of treatment (8, 9, 10).

In general, rhGH replacement therapy in adults is regarded as safe. Recently, Van Bunderen *et al.* (11) reported no differences in overall or malignancy-related mortality rate between GHD-treated patients and the background population. However, an increased risk in cardiovascular death was observed in rhGH-treated women. This increased cardiovascular mortality, however, is not easily explained. These recent findings accentuate the necessity to critically evaluate long-term efficacy and safety data.

We performed a systematic review of all available papers on long-term rhGH replacement in adult GHD patients. We aimed to evaluate the effects of long-term rhGH replacement in GHD adults on cardiovascular parameters, bone metabolism, muscle strength, QoL, mortality and adverse events.

## Materials and methods

### Search strategy and eligibility criteria

To identify studies that investigated the long-term effects of rhGH replacement in GHD adults, we searched the following databases, up to September 2012 (date of initial search 9th March, 2012): Medline, EMBASE, Web of Science and the Cochrane Library, in collaboration with a trained clinical librarian (J S). We composed a search strategy focusing on long-term rhGH treatment, GHD adults, bone metabolism, QoL, metabolic effects, muscle strength, mortality and adverse events. Chronic stable replacement was arbitrarily defined as replacement for  $\geq 5$  years, as such a period will reflect a stable metabolic situation without confounding by ongoing metabolic changes induced by the start and titration of rhGH replacement (3, 12). We used all relevant keyword variations, including free text words. Duplicated articles were excluded. The complete search strategy is provided in [Supplementary information](#), see section on [supplementary data](#) given at the end of this article. References of relevant articles were checked for additional articles. Only original articles were included.

Studies were eligible when all of the following criteria were met: i) they investigated effects on biochemical, metabolic/anthropometric parameters, bone metabolism, QoL, muscle strength, mortality, or adverse events; ii) in adult patients with either childhood-onset (CO) or adult-onset (AO) GHD; iii) with at least 5 years of rhGH treatment; and iv) were written in English. Only human studies were evaluated.

### Data extraction and analysis

Data extraction and eligibility were assessed by two independent investigators (K M J A C and N M A-D). Inconsistencies were resolved by consensus. The

following data were extracted: i) study population (patient characteristics, population size, GHD assessment, and control population); ii) exposure to rhGH (duration of rhGH treatment, and rhGH dose); iii) outcome (biochemical and anthropometric parameters, QoL, bone metabolism, muscle strength, mortality, and serious adverse events (SAEs)); and iv) potential confounders (age, sex, and CO/AO).

### Methodological quality assessment

The quality of each included paper was assessed in consensus by two independent reviewers (K M J A C and N M A-D), using a standardised set of criteria based on the STROBE statement ([Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article), which was modified to cover the topic of our review (12). A maximum score of 10 points could be obtained. According to the total quality score, articles were considered as having poor (0–2), intermediate (3–5), good (6–8), or excellent methodological quality (9–10).

## Results

### Identification and selection of the literature

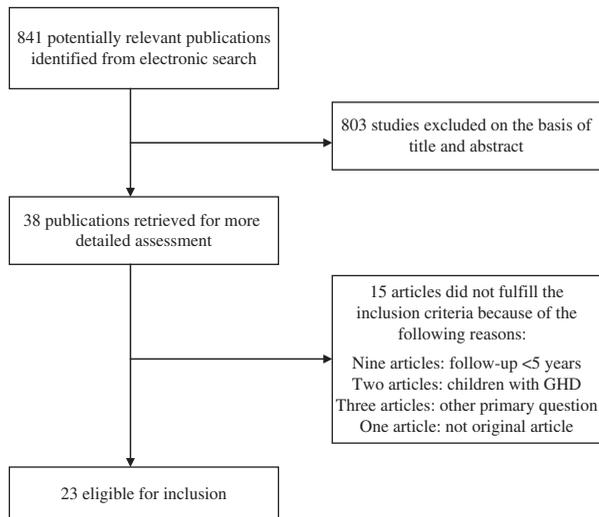
From the initial 841 potentially relevant studies identified, 803 were excluded on the basis of title and abstract. Thirty-eight papers were retrieved for detailed assessment: nine were excluded because of rhGH treatment duration  $< 5$  years, two studies described paediatric patients only, one study did not report original data and three studies did not address the long-term effects of rhGH supplementation. Consequently, 23 studies were eligible for inclusion, several describing part of the same patient cohort: (Göteborg) (4, 6, 9, 10, 13, 14, 15, 16) and (KIMS database, (5, 17)) (Fig. 1 and Table 1). Therefore, we also mention the specific study centre.

### Quality assessment

According to the predefined quality criteria, no studies were classified as being poor quality. Two studies scored intermediate (18, 19), 15 studies were good quality (4, 5, 6, 9, 11, 15, 18, 20, 21, 22, 23, 24, 25, 26, 27) and six studies had an excellent methodological quality (7, 10, 13, 15, 16, 28) (Table 1). Mean quality score was 7.3 (range 5.0–9.0), indicating that overall methodological quality was good. However, especially the items on potential bias, handling with missing data, reasons for non-participation at each study stage and the use of/handling with co-medication were not clearly described.

### Methodology

All selected studies ( $n=23$ ) were prospective follow-up studies, and eleven of these had a controlled design.



**Figure 1** Flow diagram of study selection and exclusion stages.

Healthy controls were included in six studies (5, 13, 19, 20, 21, 28), of which two studies used National Registries. Four other studies included GHD patients with intermittent rhGH treatment or untreated GHD patients as controls (11, 21, 23, 24). Gibney *et al.* (22) compared rhGH-treated patients with both untreated GHD patients and healthy controls. Four reports involved multi-centre studies (5, 11, 17, 23). No randomised controlled trials (RCT) were available.

### Endocrine evaluation

Different established stimulation tests were used for the diagnosis of severe GHD. The insulin tolerance test (ITT) was used as standard test in 16 studies and the combined GHRH–arginine test, glucagon stimulation test, or stimulation with clonidine alone, in the case of contraindications for ITT. Eight studies did not specify which stimulation tests were used (5, 11, 14, 17, 21, 23, 24, 25). Thirteen studies applied the generally used cut-off value for severe GHD of a peak GH  $< 3 \mu\text{g/l}$  (4, 6, 7, 9, 10, 13, 15, 16, 19, 22, 26, 27, 28), in seven studies no exact cut-off value was reported (5, 11, 14, 17, 21, 23, 25), and three studies used, respectively,  $< 1.7 \mu\text{g/l}$  (20),  $< 5 \mu\text{g/l}$  (18) and  $< 10 \text{ mU/l}$  (24) as cut-off. In all studies, except for one (24), information on additional pituitary deficiencies was given. Most patients had multiple anterior deficiencies, especially gonadotrope deficiency, but thyreotrope and corticotrope deficiencies were also frequently encountered.

### Duration of rhGH treatment

Mean treatment duration with rhGH ranged from 5 to 15 years: eight studies reported 5-year effects, two studies had a 6-year follow-up (11, 18), three studies investigated 7-year effects (7, 20, 27), one study

investigated the 9-year effects (24), eight studies reported 10-year effects (6, 10, 13, 14, 15, 22, 23, 25), one study described 15 years of rhGH supplementation (4). In one study, treatment duration varied among the different countries from 4 to 8 years (5).

### Dose of rhGH treatment and IGF1 levels

Fourteen studies (nine from Göteborg) calculated the GH starting dose based on body weight (4, 6, 9, 10, 13, 14, 15, 16, 19, 20, 21, 22, 24, 26). Of the remaining nine studies, three studies used dose titration of rhGH on an individual basis in the beginning of treatment, with the aim to reach IGF1 levels within the normal age- and sex-related range, and adjusted the rhGH dose accordingly (7, 28, 28). Six studies did not report their rhGH dosage regimen (5, 11, 17, 18, 23, 27). GH start dose ranged from 0.2 mg/day (7, 28) to 1.1 mg/day (20). Twelve studies reported mean GH dose after dose titration (at 1 year) (6, 9, 10, 13, 14, 15, 16, 17, 19, 20, 23, 26), ranging from 0.3 mg/day (19) to 0.85 mg/day (20) (median dose 0.54 mg/day).

Sixteen studies reported mean IGF1 levels (4, 7, 9, 10, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 27) and 13 studies described IGF1 SDS to evaluate treatment response (4, 6, 9, 10, 13, 14, 15, 16, 17, 20, 21, 23, 28) (Supplementary Table 2, see section on supplementary data given at the end of this article). Based on available IGF1 values, we can conclude that all patients were physiologically substituted at least after 5–7 years of treatment with rhGH, independently of the applied starting dosage regimen.

### Outcome of long-term rhGH replacement

**Anthropometric parameters** Thirteen studies ( $n=1185$ ) assessed the effects on body weight, BMI and/or waist-hip ratio (WHR) (4, 6, 7, 9, 10, 13, 14, 20, 23, 25, 26, 27, 28) (Table 2). rhGH supplementation did not affect WHR or waist circumference (7, 20, 25, 26, 27, 28), except for one study reporting an increased waist circumference (23). Seven studies reporting BMI found a significant increase during rhGH supplementation  $\geq 5$  years, while the other six studies reported no change (4, 6, 7, 9, 13, 14, 16, 19, 20, 23, 26, 27, 28). Two of the eight studies reporting body weight found an increase in weight during rhGH supplementation; the other studies reported no change (4, 10, 13, 14, 16, 20, 26, 27).

In conclusion, results on long-term effects on BMI appear to be inconclusive with seven studies reporting an increase and six reporting no change. In addition, there is little evidence for an increase in body weight.

**Body composition** Eleven studies ( $n=538$ ) (6, 9, 13, 14, 16, 19, 20, 22, 25, 26, 27) assessed the effects of rhGH supplementation on body composition using dual-energy X-ray absorptiometry (DEXA) scan (6, 9,

**Table 1** Included studies on the effects of long-term rhGH supplementation.

Author (ref) Center	Total (M/F) AO/CO	Mean age (year ± S.D.)	Controls	Duration of rhGH treatment (years)	Mean rhGH dose (mg/day)	Tested parameters							Quality score (points)
						Glucose	Cardio-vascular <sup>a</sup>	Anthro- pometric/ body composition <sup>b</sup>	Muscle strength	Bone	QoL	SAE/ mortality	
Gibney (22)	10 (7/3)	38 (R 21–48)	Untreated GHD (n=11) Healthy controls, age, sex and BMI matched (n=12)	10	0.025 IU/kg per day	x	x	x	x	x	x	x	7.5
Chrisoulidou (20)	12 (6/6)	52 ± 10	GHD, 0.5–1.5 years rhGH (n=11) Untreated GHD (n=10)	7	NR	x	x	x					6.5
Clanget (18)	12 (8/4) 9/3	42.5 (R 24–61)	–	6	μ 2.4 IU (0.80 mg)				x				5.0
Götherström (9) <sup>c</sup> Göteborg	118 (70/48) 118/0	49.3 (R 22–74)	–	5	0.3 (median)	x	x	x	x				7.0
Svensson (26) <sup>c</sup> Göteborg	11 (7/4) 9/2	48.0 (R 20–62)	Healthy controls, age and sex and BMI and WHR matched (n=11)	10	Initial 1.10 End 0.61	x	x	x					8.0
Gilchrist (23)	61 (27/34) 43/1	37.9 ± 11.8	Group A = continuously Group B = no Group C = inter- mittently	9	0.25 IU/kg per week					x			6.0
Svensson (17) <sup>c</sup> Göteborg	109 (61/48) 109/0	50.0 (R 22–74)	–	5	Initial 0.88 End 0.46			x	x				9.0
Svensson (27) <sup>c</sup> Göteborg	289 (186/103) 225/64	47.6 ± 14.8	National Swedish Death Registry	5	n = 80 11.9 μg/kg per day n = 209 indiv dose titration based on IGF1						x		7.5
Giavoli (19)	20 (11/9) 20/0	44 ± 14	Healthy controls, age and sex and BMI and WHR matched (n=11)	5	Initial 0.98 End 0.47	x		x					5.0
Götherström (14) <sup>c</sup> Göteborg	26 (12/14) 26/0	65.0 (R 61–74)	Reference population Göteborg	5	Initial 0.73 End 0.36			x	x				9.0
Kollowska-Hägström (5)	UK 758 (363/395) 704/54	UK 48.5 ± 12.6	General pop UK n = 892	UK 7	NR					x			7.5
KIMS database	NL 247 (123/124) 222/25	NL 48.2 ± 13.3	NL n = 1038	NL 6									
Van der Klaauw (7) <sup>d</sup> Leiden	Spain 197 (75/122) 176/21	Spain 45 ± 11.1	Spain n = 868	Spain 4									
Van der Klaauw (29) <sup>d</sup>	Sweden 484 (247/237) 453/31	Sweden 51.4 ± 13.0	Sweden n = 1682	Sweden 8									
Leiden	63 (30/33) 52/11	46.7 ± 14.3	–	7	Initial 0.2 End 0.5	x	x	x					8.5
Götherström (6) + (10) <sup>c</sup> Göteborg	50 (24/26) 50/0	45.2 ± 9.1	MORGEN cohort (n = 1062)	5	Initial 0.2	x	x	x					8.5
Cenci (28)	87 (52/35) 87/0	44.1 (R 22–74)	–	7	End 0.5 Initial 0.98			x	x				8.5
Götherström (15) <sup>c</sup> Göteborg	14 (10/4) 14/0	R 33–62	–	5	Initial 0.87 End 0.64	x	x	x					7.5
	109 (61/48) 109/0	50 R (22–74)	–	10	Initial 0.88 End 0.47	x	x	x	x				7.0

Table 1 Continued

Author (ref) Center	Total (M/F) AO/CO	Mean age (year ± s.d.)	Controls	Mean rhGH dose (mg/day)	Duration of rhGH treatment (years)	Tested parameters							Quality score (points)	
						Glucose	Cardio-vascular <sup>a</sup>	Anthro- pometric/ body composition <sup>b</sup>	Muscle strength	Bone	QoL	SAE/ mortality		
Roemmler (24) <sup>e</sup>	22 (14/8)	51.5 (R 33–75)	Untreated GHD (n=30)	0.3 (median)	10 (2–42)	x	x	x	x	x				5.5
Götherström (16) <sup>c</sup>	16/6	65.2 ± 3.4	–	Initial 0.72 End 0.37	10				x					8.5
Göteborg	24/0	F: 36.7 ± 8.4 M: 35.1 ± 8.1 (R 20–49)	–	F: initial 0.27 End 0.46 M: initial 0.31 End 0.4	10	x						x		7.5
Spielhagen (25) <sup>f</sup>	440 (224/216) 301/139													
Van Bunderen (11) <sup>g</sup>	2229 (1160/1069) 1718/511	42.6 ± 16.3	Untreated GHD (n=109) Partly treated GHD (n=356) General Dutch population Untreated GHD (n=1411)	0.3 (median) 0.48	5.7 (median)							x		7.0
Elbornsson (4) <sup>c</sup>	126 (72/54)	49.4 (R 22–74)	–	Initial 0.63 End 0.41	15			x						7.5
Göteborg	126/0													
Gaillard (21) <sup>f</sup>	13983 (7174/6809)	CO 26.9 ± 9.9 AO 48.8 ± 13.0	General reference population	NR	4.9								x	6.5
KIMS database	10767/3216													

rhGH, recombinant human GH; GHD, GH deficiency; AO, adult-onset GHD; CO, childhood-onset GHD; M, male; F, female; R, range; BF, body fat; LBM, lean body mass; ITT, insulin-tolerance test; BP, blood pressure; MS, metabolic syndrome; WHR, waist-hip ratio; carotid IMT, intima media thickness of carotid arteries; QoL, quality of life; UK, United Kingdom; NL, Netherlands; SAE, serious adverse event; NR, not reported.

<sup>a</sup>Cardiovascular: lipid metabolism, blood pressure, cardiac function, carotid IMT, or MS.

<sup>b</sup>Anthropometric: BMI, weight, WHR.

<sup>c</sup>Overlapping patient cohorts Götherström (2010), Götherström (2005), Götherström (2001), Götherström (2007), Götherström (2009), Elbornsson (2012), Svensson (2003) and Svensson (2004) (4, 6, 9, 10, 14, 15, 16, 17, 24).

<sup>d</sup>Overlapping patient cohorts Van der Klaauw (2006) and Van der Klaauw (2007) (7, 27).

<sup>e</sup>Three patients treated < 5 years.

<sup>f</sup>Overlapping patient cohorts KIMS database Kolowska-Häggström (2006), Spielhagen (2010) and Gaillard (2012) (5, 22, 26).

<sup>g</sup>Control group at baseline differed from controls at 10 years.

Table 2 Outcome of long-term rhGH therapy in GHD adults.

Outcome parameters (no. of studies)	Author (ref) Center	Total (M/F), AO/CO	Mean age (years $\pm$ s.d.)	Mean rhGH dose (mg/day)	Duration of rhGH treatment (years)	Conclusion	
Anthropometric parameters (n=13)	Chrisoulidou (21)	12 (6/6)	52 $\pm$ 10	NR	7	$\uparrow$ Weight and BMI, = WHR	
	Götherström (9) <sup>a</sup> Göteborg	118 (70/48) 118/0	49.3 (R 22–74)	0.3 (median)	5	$\uparrow$ BMI	
	Svensson (26) <sup>a</sup> Göteborg	11 (7/4) 9/2	48.0 (R 20–62)	Initial 1.10 End 0.61	10	= Weight and WHR and BMI	
	Svensson (17) <sup>a</sup> Göteborg	109 (61/48) 109/0	50.0 (R 22–74)	Initial 0.88 End 0.46	5	= Weight and BMI	
	Giavoli (28)	20 (11/9) 20/0	44 $\pm$ 14	Initial 0.98 End 0.47	5	= BMI	
	Götherström (14) <sup>a</sup> Göteborg	26 (12/14) 26/0	65.0 (R 61–74)	Initial 0.73 End 0.36	5	= Weight and BMI	
	Van der Klaauw (7) <sup>b</sup> Leiden	63 (30/33) 52/11	46.7 $\pm$ 14.3	Initial 0.2 End 0.5	7	= WC and WHR	
	Van der Klaauw (29) <sup>b</sup> Leiden	50 (24/26) 50/0	45.2 $\pm$ 9.1	Initial 0.2 End 0.5	5	$\uparrow$ BMI $\uparrow$ Waist circumference and WHR	
	Götherström (6) <sup>a</sup> Göteborg	87 (52/35) 87/0	44.1 (R 22–74)	Initial 0.98 End 0.47	7	$\uparrow$ BMI	
	Cenci (20)	14 (10/4) 14/0	R 33–62	Initial 0.87 End 0.64	5	= Weight and WC, and WHR and BMI	
	Götherström (15) <sup>a</sup> Göteborg	109 (61/48) 109/0	50 (R 22–74)	Initial 0.88 End 0.47	10	= Weight and BMI	
	Spielhagen (25) <sup>c</sup> KIMS database	440 (224/216) 301/139	$\bar{x}$ 36.7 $\pm$ 8.4 $\bar{s}$ 35.1 $\pm$ 8.1 (R 20–49)	$\bar{x}$ Initial 0.27 End 0.46 $\bar{s}$ Initial 0.31 End 0.40	10	$\uparrow$ BMI and WC, and HC = WHR	
	Elomsson (4) <sup>a</sup> Göteborg	126 (72/54) 126/0	49.4 (R 22–74)	Initial 0.63 End 0.41	15	$\uparrow$ Weight and BMI	
	Body composition (n=11)	Gibney (22)	10 (7/3) NR	38 (R 21–48)	0.025 IU/kg per day	10	= BF $\uparrow$ LBM $\uparrow$ Thigh muscle area
		Chrisoulidou (21)	12 (6/6) 10/2	52 $\pm$ 10	NR	7	$\uparrow$ BF $\uparrow$ LBM $\uparrow$ Skinfold thickness (subscap)
		Götherström (9) <sup>a</sup> Göteborg	118 (70/48) 118/0	49.3 (R 22–74)	Initial 0.98 End 0.48	5	$\uparrow$ BF
		Svensson (26) <sup>a</sup> Göteborg	11 (7/4) 9/2	48.0 (R 20–62)	Initial 1.10 End 0.61	7	$\uparrow$ LBM
		Svensson (17) <sup>a</sup> Göteborg	109 (61/48) 109/0	50.0 (R 22–74)	Initial 0.88 End 0.46	5	$\uparrow$ BF
		Giavoli (28)	20 (11/9) 20/0	44 $\pm$ 14	Initial 3–8 $\mu$ g/kg per day End 0.3	5	$\uparrow$ BF
		Götherström (14) <sup>a</sup> Göteborg	26 (12/14) 26/0	65.0 (R 61–74)	Initial 0.73 End 0.36	5	$\uparrow$ LBM
		Götherström (6) <sup>a</sup> Göteborg	87 (52/35) 87/0	44.1 (R 22–74)	Initial 0.98 End 0.47	10	$\uparrow$ BF
		Cenci (20)	14 (10/4) 14/0	R 33–62	Initial 0.87 End 0.64	5	$\uparrow$ LBM $\uparrow$ Visceral fat
		Götherström (15) <sup>a</sup> Göteborg	109 (61/48) 109/0	50 (R 22–74)	Initial 0.88 End 0.47	10	= BF $\uparrow$ LBM
Roemmier (24) <sup>d</sup>	22 (14/8) 16/6	51.5 (R 33–75)	0.3 (median)	10 (2–42)	= BF = LBM		
Lipid metabolism (n=10)	Gibney (22)	10 (7/3) NR	38 (R 21–48)	0.025 IU/kg per day	10	= TC; $\uparrow$ HDL; $\downarrow$ LDL; = TG	
	Chrisoulidou (21)	12 (6/6) 10/2	52 $\pm$ 10	NR	7	$\uparrow$ TC; = HDL; $\downarrow$ LDL; = TG	
	Götherström (9) <sup>a</sup> Göteborg	118 (70/48) 118/0	49.3 (R 22–74)	Initial 0.98 End 0.48	5	$\uparrow$ TC; $\uparrow$ HDL; $\downarrow$ LDL; = TG	
	Svensson (26) <sup>a</sup> Göteborg	11 (7/4) 9/2	48.0 (R 20–62)	Initial 1.10 End 0.61	7	= TC; $\uparrow$ HDL; $\downarrow$ LDL; = TG	
	Götherström (15) <sup>a</sup> Göteborg	109 (61/48) 109/0	50 (R 22–74)	Initial 0.88 End 0.47	10	= TC; $\uparrow$ HDL; $\downarrow$ LDL; = TG	

Table 2 Continued

Outcome parameters (no. of studies)	Author (ref) Center	Total (M/F), A/O/C	Mean age (years ± s.d.)	Mean rhGH dose (mg/day)	Duration of rhGH treatment (years)	Conclusion
Glucose (n=11)	Van der Klaauw (7) <sup>b</sup> Leiden	63 (30/33) 52/11	46.7 ± 14.3	Initial 0.2 End 0.5	7	↓ TC; ↑ HDL; ↓ LDL; = TG
	Van der Klaauw (29) <sup>b</sup> Leiden	50 (24/26) 50/0	45.2 ± 9.1	Initial 0.2 End 0.5	5	NR (TC) ↑ HDL; NR (LDL); = TG
	Götherström (6) <sup>a</sup> Göteborg	87 (52/35) 87/0	44.1 (R 22–74)	Initial 0.98 End 0.47	10	↓ TC; ↑ HDL; ↓ LDL; NR (TG)
	Cenci (20)	14 (10/4) 14/0	R 33–62	Initial 0.87 End 0.64	5	= TC; = HDL; = LDL; = TG
	Roemmler (24) <sup>d</sup>	22 (14/8) 16/6	51.5 (R 33–75)	Initial 1.10 End 0.61	10 (2–42)	= TC; = HDL; = LDL; = TG
	Spielhagen (25) <sup>c</sup> KIMS database	440 (224/216) 301/139	♀ 36.7 ± 8.4 ♂ 35.1 ± 8.1 (R 20–49)	♀ Initial 0.27 End 0.46 ♂ Initial 0.31 End 0.40	10	= TC; NR (HDL); = LDL; NR (TG)
	Gibney (22)	10 (7/3) NR	38 (R 21–48)	0.025 IU/kg per day	10	= Glucose, = insulin
	Chrisoulidou (21)	12 (6/6) 10/2	52 ± 10	Initial 0.98 End 0.48	7	= NEFA, = glucose, = insulin
	Götherström (9) <sup>a</sup> Göteborg	118 (70/48) 118/0	49.3 (R 22–74)	0.3 (median)	5	↑ Glucose, = insulin, ↓ HbA1c
	Svensson (26) <sup>e</sup> Göteborg	11 (7/4) 9/2	48.0 (R 20–62)	Initial 3–8 µg/kg per day	7	= Glucose and insulin sensitivity
	Giavoli (28)	20 (11/9) 20/0	44 ± 14	Initial 0.98 End 0.47	5	↑ Glucose and insulin
	Van der Klaauw (7) <sup>b</sup> Leiden	87 (52/35) 87/0	44.1 (R 22–74)	Initial 0.2 End 0.5	7	= HOMA-IR and QUICKI
	Van der Klaauw (29) <sup>b</sup> Leiden	50 (24/26) 50/0	45.2 ± 9.1	Initial 0.2 End 0.5	5	= Glucose
	Götherström (6) <sup>a</sup> Göteborg	63 (30/33) 52/11	46.7 ± 14.3	Initial 0.2 End 0.5	10	↑ Glucose, ↓ HbA1c
	Cenci (20)	14 (10/4) 14/0	R 33–62	Initial 0.87 End 0.6	5	= Glucose and insulin, and HOMA-IR
Roemmler (24) <sup>d</sup>	22 (14/8) 16/6	51.5 (R 33–75)	Initial 1.10 End 0.61	10 (2–42)	= All glucose parameters (including glucose, insulin, HbA1c, insulin sensitivity, insulin resistance, β-cell-function, and HOMA)	
Spielhagen (25) <sup>c</sup> KIMS database	440 (224/216) 301/139	♀ 36.7 ± 8.4 ♂ 35.1 ± 8.1 (R 20–49)	♀ Initial 0.27 End 0.46 ♂ Initial 0.31 End 0.40	10	= Glucose	
Cardiovascular parameters (including metabolic syndrome (n=8))	Gibney (22)	10 (7/3) NR	38 (R 21–48)	0.025 IU/kg per day	10	= SBP and DBP = LVM and ESM, and EDM ↓ Carotid IMT
	Chrisoulidou (21)	12 (6/6) 10/2	52 ± 10	NR	5	= SBP and DBP = IVRT, = LVM = HR, ↓ resting DBP, = SBP = Exercise time = SBP and DBP
	Van der Klaauw (7) <sup>b</sup> Leiden	63 (30/33) 52/11	46.7 ± 14.3	Initial 0.2 End 0.5	7	= SBP and DBP
	Van der Klaauw (29) <sup>b</sup> Leiden	50 (24/26) 50/0	45.2 ± 9.1	Initial 0.2 End 0.5	5	↑ MS prevalence
	Cenci (20)	14 (10/4) 14/0	R 33–62	Initial 0.87 End 0.64	5	↓ Carotid IMT
Neuromuscular function (n=5)	Gibney (22)	10 (7/3) NR	38 (R 21–48)	0.025 IU/kg per day	10	= Muscle strength
	Svensson (17) <sup>a</sup> Göteborg	109 (61/48) 109/0	50.0 (R 22–74)	Initial 0.88 End 0.46	5	↑ Knee flexor and extensor strength ↑ Hand grip strength
	Götherström (14) <sup>a</sup> Göteborg	26 (12/14) 26/0	65.0 (R 61–74)	Initial 0.73 End 0.36	5	↑ Knee flexor and extensor strength ↑ Peak hand grip strength
	Götherström (15) <sup>a</sup> Göteborg	109 (61/48) 109/0	50 (R 22–74)	Initial 0.88 End 0.47	10	↑ Knee flexor and extensor strength ↑ Hand grip strength
	Götherström (16) <sup>a</sup> Göteborg	24 (11/13) 24/0	65.2 ± 3.4	Initial 0.72 End 0.37	10	↑ Knee flexor strength ↑ Hand grip strength = Muscle endurance

Table 2 Continued

Outcome parameters (no. of studies)	Author (ref) Center	Total (M/F), AO/CO	Mean age (years $\pm$ s.d.)	Mean rhGH dose (mg/day)	Duration of rhGH treatment (years)	Conclusion
Bone (n=5)	Clanget (19) Götherström (9) <sup>a</sup> Göteborg Götherström (10) <sup>a</sup> Göteborg Roemmier (24) <sup>d</sup> Elbomsson (4) <sup>a</sup> Göteborg	12 (8/4) 9/3 118 (70/48) 118 87 (52/35) 87/0 22 (14/8) 16/6 126 (72/54) 126/0	42.5 (R 24–61) 49.3 (R 22–74) 44.1 (R 22–74) 51.5 (R 33–75) 49.4 (R 22–74)	$\mu$ 2.4 IU (0.80 mg) Initial 0.98 End 0.48 Initial 0.98 End 0.47 0.3 (median) Initial 0.63 End 0.41	6 5 10 10 (2–42) 15	$\uparrow$ BMC and BMD (lumbar spine, trochanter, = femur neck) $\uparrow$ BMC and BMD = Osteocalcin and Ca <sup>2+</sup> and PTH $\uparrow$ BMC and BMD (total body, lumbar spine, prox femur) $\uparrow$ Osteocalcin and Ca <sup>2+</sup> = BMD $\uparrow$ BMC and BMD (total body, lumbar spine, plateau) $\uparrow$ BMC = BMD (prox femur, peak at 7 years, thereafter $\downarrow$ ) Fractures: $\uparrow$ hip, $\uparrow$ symp VF $\uparrow$ Overall psychological well-being, energy, emotional reaction NHP: $\uparrow$ energy levels, = sleep and emotional reaction and social isolation and physical mobility and pain PGWB: $\uparrow$ vitality score QoL-AGHDA: $\uparrow$ in 1st year, after that regression to country-specific mean (normalization)
Quality of life (n=4)	Gibney (22) Gilchrist (23) Koltowska-Hägström (5) <sup>c</sup> KIMS database	10 (7/3) NR 61 (27/34) 43/1 UK 758 (363/395) 704/54 NL 247 (123/124) 222/25 Spain 197 (75/122) 176/21 Sweden 484 (247/237) 453/31 440 (224/216) 301/139	38 (R 21–48) 37.9 $\pm$ 11.8 UK 48.5 $\pm$ 12.6 NL 48.2 $\pm$ 13.3 Spain 45 $\pm$ 11.1 Sweden 51.4 $\pm$ 13.0 $\mu$ 36.7 $\pm$ 8.4 $\sigma$ 35.1 $\pm$ 8.1 (R 20–49) End 0.46 $\sigma$ Initial 0.31 End 0.40	0.025 IU/kg per day 0.25 IU/kg per week NR	10 9 UK 7 NL 6 Spain 4 Sweden 8 10	
Mortality/SAE (n=3)	Svensson (27) <sup>a</sup> Göteborg Van Bunderen (11) Gaillard (18) <sup>c</sup> KIMS database	289 (186/103) 225/64 2229 (1160/1069) 1718/511 13 983 (7174/6809) 10 767/3216	47.6 $\pm$ 14.8 42.6 $\pm$ 16.3 CO 26.9 $\pm$ 9.9 AO 48.8 $\pm$ 13.0	n=80 (11.9 $\mu$ g/kg per day) n=209 (individual dose titration based on IGF-1) $\mu$ 0.48 NR NR	5 5.7 (median) 4.9	= Overall mortality and malignancy rate $\downarrow$ MI rate, $\uparrow$ CVA rate = Mortality compared with background pop (after exclusion high-risk) = Malignancy mortality $\uparrow$ CVD mortality in $\sigma$ $\uparrow$ Overall mortality in $\sigma$ (moderate) = Malignancy and CVD mortality $\uparrow$ CVA and infection mortality $\uparrow$ Progression primary tumour and endocrine complications

rhGH, recombinant human GH; GHD, GH deficiency; AO, adult-onset GHD; CO, childhood-onset GHD; R, range; BF, body fat; LBM, lean body mass; ITT, insulin-tolerance test; GHRH, GH releasing hormone; BMD, bone mineral density; BMC, bone mineral content; TG, triglycerides; BP, blood pressure; MS, metabolic syndrome; WC, waist circumference; HC, hip circumference; WHR, waist:hip ratio; HOMA-IR, homeostasis model assessment of insulin resistance; QUIJKI, quantitative insulin check index; Carotid IMT, intima media thickness of carotid arteries; QoL, quality of life; NHP, Nottingham Health Profile; PGWB, psychological general well-being schedule; QoL-AGHDA, quality of life-assessment of GH deficiency in adults; LVM, left ventricular mass; ESM, end systolic diameter; EDM, end diastolic diameter; Ca<sup>2+</sup>, calcium; NEFA, nonesterified fatty acids; Lp(a), lipoprotein (a); APU, apparent phalangeal ultrasound transmission velocity; CVD, cardiovascular disease; IVRT, isovolumic relaxation time; LVM, left ventricular mass; VF, vertebral fracture; UK, United Kingdom; NL, The Netherlands; MI, myocardial infarction; CVA, cerebrovascular attack; SAE, serious adverse event; NR, not reported.

<sup>a</sup>Overlapping patient cohorts Götherström (2001, 2005, 2007, 2009, 2010), Svensson (2003, 2004), and Elbomsson (2012).

<sup>b</sup>Overlapping patient cohorts KIMS database Koltowska-Hägström (2006), Spielhagen (2011), and Gaillard (2012).

<sup>c</sup>Three patients treated <5 years

<sup>d</sup>Control group at baseline differed from controls at 10 years.

13, 14, 16, 25, 27), bioelectrical impedance analysis (BIA) (19, 20), or a heliocidal CT scan (26). Gibney *et al.* (22) measured body composition with radioisotope potassium. The majority of studies ( $n=9$ ) reported consistent effects with an increase in LBM and a decrease in total body fat (BF) (6, 9, 13, 14, 16, 19, 20, 22, 27). One study could not detect any effect of rhGH on body composition (25). Cenci *et al.* (26) reported only a decrease in visceral fat.

In conclusion, rhGH supplementation had favourable effects on body composition, with an increase in LBM and a decrease in total BF. Several methods are available to evaluate body composition, which may account for differences between studies. These differences might have influenced the results significantly. In the literature, DEXA is reported to be the best currently available technique for measuring body composition (29); however, in this respect, it has to be noted that DEXA cannot distinguish between body cell mass (BCM) and water. Therefore, the LBM data may not be accurate, as rhGH replacement is associated with an increase in the intracellular water component (30, 31, 32, 33). However, also when using other modalities to evaluate body composition, positive long-term effects of rhGH replacement were found.

**Lipid metabolism** Ten studies ( $n=827$ ) assessed the effects of rhGH supplementation on fasting plasma lipid profiles (6, 7, 9, 20, 22, 23, 25, 26, 27, 28). Three studies did not find any effect of rhGH therapy on plasma lipids (23, 25, 26). The seven remaining studies reported generally similar results, i.e. reduction of TC and LDL-C, an increase in HDL-C and no effect on triglycerides (6, 7, 9, 20, 22, 27, 28). In six patients, new-onset hyperlipidaemia was reported (Göteborg). However, only four studies reported the number of patients on lipid-lowering medication, especially statins (6, 7, 25, 28), but without excluding these patients from analysis.

In summary, there are ongoing beneficial effects of rhGH supplementation on plasma lipids. However, a strong limitation is the lack of data concerning lipid-lowering treatment, which has a considerable influence on the outcome parameter. Due to the lack of information on lipid-lowering drugs and the overlap in patient groups, meta-analysis was not an option.

**Glucose metabolism** Eleven studies ( $n=847$ ) assessed the effects of rhGH supplementation on glucose and insulin levels (6, 7, 9, 19, 20, 22, 23, 25, 26, 27, 28). Seven studies showed no effect on glucose (7, 22, 23, 25, 26, 27, 28), three an increase (6, 9, 19) and one study found a transient increase in glucose levels only during the first year of rhGH therapy (20). Insulin levels increased only in one study (19). HbA1c was evaluated in three studies, two of which observed a decrease (6, 9); the other found no change (25). Three studies investigated insulin resistance by the homeostasis

model assessment (HOMA) (19, 25, 26), reporting no significant effects of rhGH supplementation. Insulin sensitivity was not affected in two studies (20, 25), while another study reported a transient decrease, using the quantitative insulin check index (QUICKI), showing a trend to return towards basal values afterwards (19). In at least ten patients, new-onset diabetes mellitus type 2 (DM2) was diagnosed (four Göteborg, six KIMS (23)). Five studies reported the number of patients starting anti-diabetic medication during follow-up (6, 9, 20, 25, 26). Only one study excluded diabetic patients from analysis (9), while the other studies did not report the handling with anti-diabetic medication in their statistical analysis.

In conclusion, there is moderate evidence for an increase in mean glucose levels after chronic rhGH treatment; however, insulin sensitivity appeared not to be affected in the long term. Due to the lack of information on anti-diabetic medication and the overlap in patient cohorts, we were not able to perform a meta-analysis on this parameter.

**Cardiovascular parameters** Four studies ( $n=135$ ) investigated the effects of rhGH supplementation on blood pressure (7, 9, 22, 27, 28). No effect was found on systolic blood pressure (SBP); one study reported a decrease in resting DBP (27). Only two studies described the number of patients on antihypertensive medication (7, 28), without excluding them from analysis. Prevalence of the metabolic syndrome (MS) was assessed in one study, reporting a strong increase when compared with healthy controls, despite 5 years of rhGH treatment (38.0 vs 15.7%) (28).

Two studies ( $n=22$ ) evaluated the long-term effects on cardiac function (22, 27) using echocardiography; Chrisoulidou *et al.* (27) also performed an exercise test. Left ventricular mass (LVM) was not affected. In addition, no effect on end diastolic or systolic diameter (22) nor on isovolumetric relaxation time (IVRT) or LVM was demonstrated (22, 27). Two studies ( $n=24$ ) evaluated carotid intima media thickness (IMT), reporting a decrease in IMT up to 18% after long-term rhGH therapy (22, 26).

In conclusion, no effect on SBP of LVM was reported. In addition, conclusions on the prevalence of MS cannot be made, as this parameter was only evaluated in one study. Long-term rhGH supplementation had positive effects on IMT.

**Muscle strength** Five studies ( $n=278$ , all AO-GHD) investigated the effects of rhGH supplementation on muscle strength (13, 14, 16, 22). In general, 5 years of rhGH improved knee flexor and extensor and hand-grip strength. However, these effects were not sustained after 10 years. One study also investigated muscle endurance; no significant effects of rhGH supplementation were demonstrated (15). In addition, rhGH supplementation did not affect muscle strength in the elbow, shoulder, or

hip (22). Compared with population-based controls, rhGH was found to be protective to the normal age-related decline in muscle performance and neuromuscular function (13, 14).

In general, rhGH supplementation improved muscle strength during the first 5 years of treatment; however, these effects were not sustained after prolonged follow-up. As almost all studies described one patient group, we were not able to perform a meta-analysis on this parameter.

**Bone parameters** Four studies ( $n=343$ ) evaluated the long-term effects of rhGH on bone (4, 9, 10, 18). After an initial decline, all studies reported an increase in both BMD and BMC within the first 5 years of treatment. After 5 years, all studies reported a plateau phase, which lasted for the entire study period (i.e. sustained effects) (4, 9, 10, 18). Only one study investigated (symptomatic) fracture prevalence, reporting one hip fracture and one symptomatic vertebral fracture (4). None of the studies described the use of calcium or vitamin D supplementation, or the use of bisphosphonates, selective estrogen receptor modulator (SERM), teriparatide, or strontium ranelate. Again, most patients were from the same study centre, prohibiting the performance of a meta-analysis.

**Quality of life** Two large cohort studies (both KIMS database,  $n=1686$  and  $n=440$  respectively) and two smaller studies ( $n=71$ ) addressed the effects on QoL and neuropsychological well-being, by QoL-Assessment of GHD in Adults (QoL-AGHDA), Nottingham Health Profile (NHP) and Psychological General Well-Being (PGWB) questionnaires (5, 22, 23, 24). Within the first year of treatment, a direct beneficial response on well-being was noticed, as assessed by QoL-AGHDA, with marginal changes after the dose-titrating phase (5, 23). Improvement was related to the degree of QoL impairment at baseline (5). Scores on NHP and PGWB improved in the long-term, especially with respect to energy level and emotional reaction (22, 24).

In conclusion, QoL seemed to improve during long-term rhGH replacement, but positive effects on QoL were especially seen within the first year of treatment. As studies are scarce and none of them had a placebo-controlled randomised controlled design, which is of paramount importance for the interpretation of QoL, no firm conclusions can be drawn on the effects of long-term rhGH replacement on QoL.

**Effects of rhGH on mortality** Three cohort studies ( $n=16\ 501$ ) reported data on mortality after long-term rhGH supplementation (11, 17, 21), of which one study reports KIMS data ( $n=13\ 983$ ). In Gaillard *et al.* (17), overall mortality rate was moderately increased, especially in females, young attained age, patients with aggressive tumours and lower IGF1 SDS during

therapy. The other studies did not report differences in overall mortality or malignancy-related death. In two studies (17, 21), the rate of cerebrovascular accidents (CVAs) was increased, but the incidence of myocardial infarction was decreased (risk ratio (RR) 0.27, 95% CI 0.03–0.99) when compared with the background population (21). In addition, rates of death due to infections (standardised mortality ratio (SMR) 4.97, 95% CI 3.98–6.14), primary tumour progression (SMR=6.96, 95% CI 4.45–10.3) and endocrine complications (SMR=2.79, 95% CI 1.30–5.23) were increased (17). Van Bunderen *et al.* (11) ( $n=2229$ ; median rhGH treatment of 5.7 years) reported an increase in cardiovascular-related deaths in GHD-treated women (SMR 2.36). This was not supported by the other long-term studies (17, 21).

In summary, there is evidence for a moderate increased mortality rate despite long-term rhGH replacement, especially in females. Differences in pituitary disease, hormone replacement- and radiation therapies may account for differences between studies. However, as long-term studies on mortality are scarce, at this moment, no firm conclusions on the safety of long-term rhGH replacement can be drawn.

### Serious adverse events

Twelve studies reported SAEs during long-term rhGH treatment ( $n=9$  from Göteborg) (4, 6, 7, 9, 13, 14, 15, 16, 20, 23, 27). As several studies described the same patient cohort, the total number of SAEs could not be extracted.

**Malignancies** A total of six malignancy cases were reported in the GHD cohort of Göteborg: colonic carcinoma ( $n=1$ ), prostate carcinoma ( $n=1$ ), chronic lymphatic leukaemia ( $n=1$ ), renal carcinoma ( $n=1$ ), bladder carcinoma ( $n=1$ ) and pulmonary carcinoma ( $n=1$ ). In addition, 12 cases of *de novo* malignancies, not further specified, were reported (7, 23).

**Cardiovascular events** Three cases of myocardial infarction (Göteborg, Van der Klaauw *et al.* (7)) were reported, of which two with fatal outcome. Five patients suffered from a CVA (Göteborg, Van der Klaauw *et al.* (7)), resulting in death in four cases, and one patient died from a subarachnoid haemorrhage (Göteborg). In addition, angina pectoris was reported ( $n=3$ ) (Göteborg), and one patient died from a pulmonary embolism (Göteborg). In at least ten patients, new-onset DM2 was diagnosed (four Göteborg, six KIMS (23)). New-onset hyperlipidaemia and hypertension were reported in six and four patients respectively (Göteborg (27)).

**Other SAEs** Two studies reported primary tumour growth ( $n=11$ ), either recurrence of the pituitary or CNS tumour (7, 23).

In conclusion, half of the studies reported SAEs during rhGH therapy. Due to the lack of a control group including non-treated GHD patients, no firm conclusions can be drawn.

## Discussion

The short-term effects of rhGH treatment are well-established, showing favourable effects of rhGH therapy within the first 3 years on body composition, lipid profile, bone turnover, BMD, muscle strength, cognitive function and QoL. This is the first systematic review focusing on the long-term effects of rhGH treatment (beyond  $\geq 5$  years of treatment). Overall, long-term rhGH therapy beneficially affected QoL and BMD. In addition, sustained beneficial effects were reported on lipid spectrum and on carotid IMT after 10 years of treatment. Consistent effects on body composition were reported with an increased LBM and a decreased total BF. Muscle strength increased after 5 years of rhGH supplementation, but these effects were not sustained during longer follow-up. Negative effects were reported on mean glucose levels; however, insulin sensitivity appeared not to be affected by long-term rhGH treatment.

The effects of rhGH replacement on bone turnover, and thus on BMD, are dynamic over time. Initially, BMD decreases due to increased bone resorption and formation, followed by an increase within the first years of treatment, finally resulting in a plateau phase. The five studies addressing this topic showed a significant increase within the first 5 years of treatment. Thereafter, BMD was conserved but did not further increase (4, 9, 10). Only one study described the number of symptomatic fractures (4), however, without radiographic assessment of the vertebral column. As a consequence, the reported fracture rate is most probably underestimated, as 21% of the fractures in patients with osteopaenia or osteoporosis are asymptomatic (34). Fracture incidence was also studied by Holmer *et al.* (35), but a considerable proportion of patients was treated for < 5 years. In CO-GHD women, but not in AO-GHD women or CO-GHD men, fracture risk was doubled, and in men with AO-GHD fracture incidence was even decreased (35). Further research has to establish the efficacy of rhGH treatment with respect to fracture risk.

Presently, in clinical practice, QoL is the most frequently addressed outcome parameter, but in the long-term, QoL was studied only in four studies (5, 22, 23, 24). The two largest studies (KIMS database) showed improvement within the first year of treatment, with thereafter steady progress towards the country-specific mean (i.e. normalisation) (5, 23). The other two studies found ongoing beneficial effects on energy level and emotional reaction (22, 24). Unfortunately, none of these studies had a placebo-controlled randomised controlled design. Thus, based on current literature,

long-term effects on QoL are inconclusive, and therefore, in daily clinical practice, QoL should be individually evaluated in each patient.

With respect to plasma lipids, seven out of ten studies investigating the long-term effects of rhGH replacement on the lipid profile report ongoing beneficial effects, with a reduction of TC and LDL-C levels, an increase in HDL-C and no effect on triglycerides. However, in this respect, a strong limitation is the lack of data concerning lipid-lowering treatment, prohibiting to draw firm conclusions on this outcome parameter. When comparing these long-term results to short-term studies on plasma lipids, it has been noted that there were also several (randomised controlled) short-term studies reporting no change or minimal effects on lipid levels, and that even these effects were limited to men (36, 37). Overall, however, as shown in a meta-analysis of Maison *et al.* (3) investigating 37 placebo-controlled randomised controlled studies (follow-up for up to 18 months), rhGH replacement was shown to improve LDL-C and TC levels in the short-term.

Concerning the safety of rhGH supplementation, in children, long-term safety data have been conflicting, raising the question of whether long-term use of rhGH is safe. Several large studies did not find an increased mortality in paediatric GHD patients after rhGH replacement, especially not due to new-onset malignancies or recurrence of CNS tumours. Cause of death was assessed as unrelated to rhGH replacement in the majority of patients (38, 39, 40, 41, 42). In contrast, a recent study of Carel *et al.* (43) showed an increased incidence in bone tumour-related mortality and mortality due to cardiovascular diseases in a large cohort of French children, especially in those with the highest GH doses ( $> 50 \mu\text{g}/\text{kg}$  per day). Cancer mortality was also increased in a large paediatric UK cohort, especially in high-risk patients (44). Moreover, Bell *et al.* (38) reported an increase in the occurrence of second tumours in children with a prior history of malignancy, especially in case of prior exposure to radiotherapy. These discrepant results could be possibly explained by the different dosage regime, with higher GH doses in the French study. A recent meta-analysis underlines this hypothesis, establishing that both low and high IGF1 levels are associated with increased mortality (hazard ratio (HR) 1.18, 95% CI 1.04–1.34) (45). Adult studies did not show an increased mortality or malignancy rate (11, 21), except for one study showing a moderate increase in overall mortality in females (17). However, the studies do not represent unselected patients, as initiation of rhGH replacement is not likely in patients with an a priori increased cancer risk, thus creating a clear selection bias. With respect to cardiovascular outcomes, an increase in cardiovascular deaths and number of CVAs was reported in women, whereas the myocardial infarction rate decreased (11, 17, 21). The increased incidence in cardiovascular deaths in women might partly be attributed to the more

atypical presentation of cardiovascular diseases in women (46). Other factors such as inadequately substituted hypogonadism causing preterm menopause or hypocortisolism may also have influenced this risk. In this respect, it has to be noted that available data suggest that both mortality risk and the causes for mortality are related in both patients receiving and those not receiving rhGH replacement. However, it is of paramount importance to accentuate that all observed increased mortality rates reported to date have been associated only with the presence of hypopituitarism *per se*, but that it is still uncertain if, and to what extent, this can be attributed to GHD.

We assessed the methodological quality of all studies using a modified STROBE list (12), classifying 21 of the 23 included studies as having a good or excellent methodological quality. Several quality criteria were not clearly described; specifically, information on potential bias, handling with missing data and reasons for dropout was lacking in most studies. In addition, the use of co-medication, especially lipid-lowering and anti-diabetic drugs, was not clearly reported. It is of importance to emphasise this limitation, because the effects of rhGH therapy on lipid profile, glucose levels and other cardiovascular parameters could not be interpreted without this information. In addition, no RCTs were identified with a follow-up duration > 5 years and only a limited number of centres have reported their data, with half of the long-term studies describing (part of) the same patient cohort (Göteborg). Other studies were relatively small and might have been, therefore, underpowered to allow firm conclusions. Due to these limitations, we were not able to perform a meta-analysis.

Another limitation is the report of outcomes only for patients who had completed 5 or 10-years of follow-up, instead of describing the original cohort. This may introduce a significant selection bias, as patients discontinued rhGH therapy for specific reasons and, therefore, are likely to differ from patients with complete follow-up. Furthermore, a major limitation of most studies is the lack of a control group and thereby the lack of control for ageing. This limitation is important to notice when interpreting the long-term effects of rhGH replacement on, for example, body weight, BMI, blood pressure, lipid profile, body composition and BMD (47, 48, 49). Consequently, it is very difficult to discriminate between effects as a consequence of natural ageing processes and effects by rhGH replacement *per se*. Firm conclusions on the effects of rhGH *per se* can therefore not be drawn from present results. Another feature that needs to be addressed is the change in patient characteristics and approach to rhGH supplementation over time, which may represent an important confounder for any analysis (50). This emphasises the need for ongoing monitoring during rhGH treatment.

In summary, available literature on long-term rhGH replacement in adult GHD patients shows inconsistent results with respect to its expected beneficial effects, in

the presence of several drawbacks to enable a definite interpretation. First, long-term studies were generally uncontrolled and lacked a control group (of non-treated GHD patients) enabling adjustment for subjective changes or changes due to ageing. Second, only a limited number of centres have reported their data, resulting in a low number of evaluable patients with a follow-up duration of  $\geq 5$  years of rhGH replacement with half of the long-term studies describing (part of) the same patient cohort. Especially the course of QoL during ongoing therapy is unestablished. With respect to the metabolic profile, rhGH therapy has shown prolonged, beneficial effects in the long-term for body composition, lipid profile, carotid IMT and BMD, but overall cardiovascular risk, as assessed by the prevalence of the MS, glucose levels and BMI appeared not to be influenced or was even negatively affected. Therefore, the benefit of long-term rhGH treatment should be a matter of ongoing research to enable adequate risk-benefit analyses and, in clinical daily practice, the benefits of rhGH should be considered carefully in each patient.

### Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-12-1088>.

### Declaration of interest

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

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