

# Effects of discontinuation of growth hormone replacement in adult GH-deficient patients: a cohort study and a systematic review of the literature

Natasha M Appelman-Dijkstra<sup>1</sup>, Marnick Rijndorp<sup>1</sup>, Nienke R Biermasz<sup>1</sup>,  
Olaf M Dekkers<sup>1,2,3</sup> and Alberto M Pereira<sup>1</sup>

<sup>1</sup>Department of Medicine, Division of Endocrinology and Center for Endocrine Tumors, Leiden University Medical Center, Leiden, The Netherlands, <sup>2</sup>Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands and <sup>3</sup>Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark

Correspondence should be addressed to N M Appelman-Dijkstra  
Email  
[n.m.appelman-dijkstra@lumc.nl](mailto:n.m.appelman-dijkstra@lumc.nl)

## Abstract

**Background:** Recombinant human growth hormone (rhGH) replacement is advocated in adult growth hormone-deficient (GHD) patients to increase bone mass and improve lipid profile, body composition, and quality of life. The long-term effects of discontinuation of rhGH replacement are unknown.

**Methods:** This cohort study and systematic review aim to evaluate the long-term metabolic effects of discontinuation of rhGH replacement in adult GHD patients, with a subgroup analyses according to age (< or > 60 years). Data on anthropometry, lipids, glucose, and bone mass density (BMD) were assessed for 3 years after discontinuation.

**Results:** Cohort study included 64 patients who had discontinued rhGH replacement for >12 months. Fat percentage increased from  $31.5 \pm 9.5\%$  to  $33.8 \pm 9.0\%$  (mean difference 2.3,  $P=0.003$ ). BMI decreased only in subjects <60 years ( $P=0.014$ ). Glucose, total cholesterol, and LDL-cholesterol levels did not change; however, the percentage of patients on statins increased slightly from 39% to 44%. HDL-C concentration increased only in patients <60 years (mean difference 0.2,  $P=0.043$ ). Lumbar spine BMD did not change; however, femoral neck BMD and bone turnover markers decreased in subjects <60 years ( $P=0.001$ ). Systematic review included eight studies ( $n=166$  patients) with a follow-up duration of 6–18 months. Of the eight studies, three qualified as low risk of bias and five as having an intermediate risk of bias. None of the studies reported handling of statins, bisphosphonates, and glucose-lowering medication or excluded patients using these medications.

**Conclusions:** In this study, discontinuation of rhGH replacement resulted in metabolic changes only in patients <60 years after 3 years. Further research warrants to determine the optimal strategies for (dis)continuation of rhGH replacement in adult patients with GHD.

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## Introduction

Adult growth hormone deficiency (GHD) is associated with an adverse metabolic profile, including abdominal obesity, dyslipidemia, and an increased cardiovascular mortality risk (1, 2). In addition, several studies have

demonstrated that adult GHD patients have lower bone mass, increased fracture risk, and impaired quality of life (QoL) (3, 4). Recombinant human growth hormone (rhGH) replacement therapy has shown to improve lipid

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profile, body composition, and QoL, to increase bone mass, and is available for adult patients with GHD for two decades now (5, 6, 7, 8, 9, 10). Long-term follow-up studies, however, have shown that the prevalence of the metabolic syndrome does not ameliorate, and BMI even increases while on rhGH replacement. More specifically, in a previous study of our group on the long-term rhGH use, we found that despite 5 years of rhGH replacement, the metabolic profile of GHD patients remained different and the metabolic syndrome was more prevalent in patients than in general population (8, 11, 12).

Another topic that has not yet been well established is the optimal duration of rhGH replacement in advanced age and the consequences of rhGH withdrawal in adulthood. However, in case of an active malignancy or lack of subjective benefit, it is advised to stop rhGH replacement (13). As GH secretion and IGF-1 levels decrease in healthy adults with advancing age and low IGF-1 levels are even associated with increased longevity and decreased morbidity both in animal models and in humans, it is questionable whether the beneficial effects of rhGH replacement will be sustained in elderly patients (14, 15). Studies reporting on the efficacy of rhGH replacement in elderly (>60 years) GHD patients are limited and show inconclusive results, and data on rhGH discontinuation in adult GHD are scarce (16).

In this study, we aimed to evaluate the metabolic effects of discontinuation of rhGH replacement in our cohort of adult GHD patients in general and in the subset of patients aged 60 years or older. At our center, the duration of rhGH replacement is individualized; however, rhGH replacement is discontinued in case of malignancy and side effects, and withdrawal is considered in case of lack of subjective benefit and at an advanced age.

Furthermore, we performed a systematic review of studies reporting on the effects of discontinuing rhGH replacement in adults.

## Patients and methods

### Cohort study

#### Patients

Patients were identified from the database of the Leiden cohort of adult patients with GHD. The LUMC ethics committee approved the collection of these anonymous patient data. This cohort comprised all patients starting rhGH since 1994, who were subjected to standardized evaluation of clinical and metabolic parameters annually

at the outpatient clinic of the Center for Endocrine Tumors (8, 11, 12, 17, 18, 19).

We performed a cohort study that specifically aimed to evaluate the metabolic effects of rhGH discontinuation. For the present analyses, we included all GHD patients treated continuously with rhGH for at least 12 months during adulthood and who discontinued rhGH replacement therapy for at least for 12 months, irrespective of the reason for discontinuation. Patients with a baseline visit before discontinuation and at least one follow-up visit after discontinuation were included.

The baseline visit was defined as the last visit before discontinuation of rhGH replacement. Data were assessed at baseline and at 1, 2, and 3 years thereafter.

The following data were assessed during the periodical visits:

1. Anthropometric parameters: body weight was measured in kilograms with 1 decimal precision, and body height was measured barefoot to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ). Physical and psychological well-being was monitored during all follow-up visits.
2. Biochemical parameters: serum concentrations of IGF-1, GH, bone turnover markers procollagen type 1 N-terminal propeptide (P1NP) and beta crosslaps, PTH, vitamin D, glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were collected after an overnight fast. Details on the different assays used were reported previously (8).
3. Bone mineral density and body composition: data on BMD, BMC, and fat percentage were collected. BMD was measured at the lumbar spine (L1–L4) and femoral neck using dual-energy X-ray absorptiometry (DXA; Hologic QDR 1000 (until 2008) and Hologic QDR 4500 (thereafter); Hologic Inc., Waltham, MA, USA) equipped with reference values based on the National Health and Nutrition Examination Survey (NHANES III) from the time of start of rhGH replacement onward. Coefficient of variation of lumbar spine and femoral neck BMD measurements was 1%. An in-house comparison using 300 measurements provided a conversion formula for comparison with the laterly acquired Hologic 4500 BMD measurements. World Health Organization (WHO) criteria were used to define osteopenia ( $T$ -score between  $-1.0$  and  $-2.5$ ) and osteoporosis ( $T$ -score  $\leq -2.5$ ). BMC was measured at the lumbar spine using the same DXA apparatus (20). Fat percentage was assessed by calculating the total mass of fat divided by total body mass.

4. Data on medication use and co-morbidity were obtained from electronic patient files.
5. Fracture data: specific information on clinical fractures was retrieved from the medical charts. No routine spine radiographs were performed to assess the presence of vertebral fractures; however, radiographs were made in case of height loss >3 cm or specific complaints at the discretion of the treating physician.

#### *The diagnosis and treatment protocol of adult patients with GHD*

All patients that fulfilled the criteria for the diagnosis of adult GHD are offered treatment with rhGH in The Netherlands, provided that no absolute contraindications are present. In all cases, GHD was documented before start of rhGH replacement according to the international guidelines and when stimulation tests were performed. Severe GHD was defined as a GH peak response to the insulin tolerance test (ITT) <3 µg/L (glucose nadir <2.2 mmol/L) or, in case of contraindications for ITT, by the peak response to combined growth hormone-releasing hormone/arginine stimulation (GHRH/Arg) with BMI-adjusted GH cutoffs (21, 22, 23, 24, 25, 26). Of all the patients, 41 were diagnosed as GHD by insulin tolerance test and 20 by GHRH+arginine. Patients receiving rhGH replacement during childhood were retested at the time of transition to adult care, after treatment discontinuation for at least 3 months. All patients started on rhGH therapy were treated according to a pre-specified institutional protocol that has been used since the early 1990s (17, 18). The initial dose of rhGH was 0.2 mg/day, which was individually adjusted each month in the first half year to achieve serum IGF-1 concentrations within the age-dependent laboratory reference range, aimed at SDS between 0 and +2. When stable plasma concentrations were reached, this individualized dose was continued and adjusted if necessary. Hormone deficiencies were diagnosed and treated as previously reported (8, 20). Adjunctive medication, such as bisphosphonates, calcium and vitamin D replacement, and lipid-lowering and antihypertensive medication, was continued after withdrawal of rhGH replacement. Efficacy and safety parameters were assessed yearly, next to a routine assessment of pituitary hormones and their replacement.

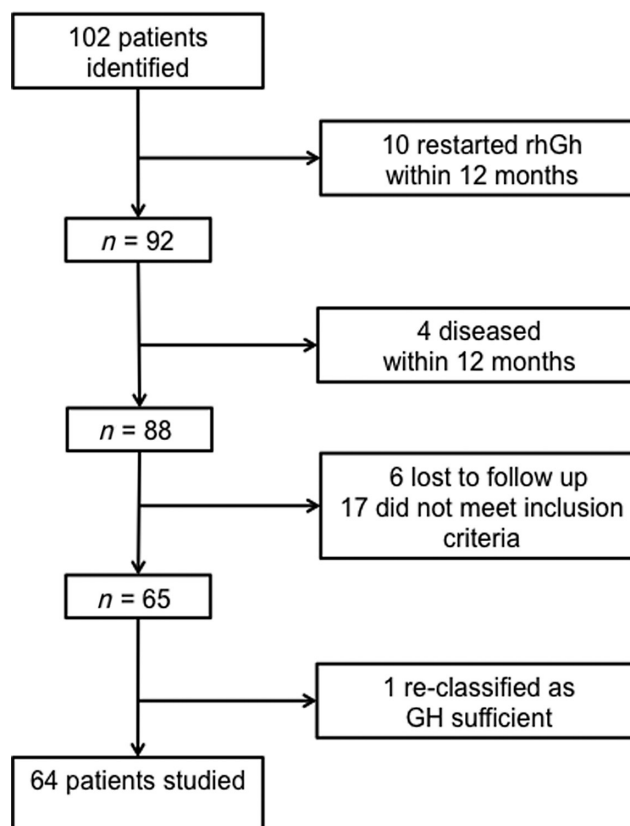
#### *Clinical characteristics*

In total, 102 patients were identified who discontinued therapy. Of these, four patients died before the first

annual visit after discontinuation of rhGH replacement, ten patients re-initiated rhGH replacement within the first year, six patients were lost to follow up, and 18 patients did not meet the inclusion criteria (Fig. 1).

A total of 64 patients (mean age  $59.7 \pm 15.7$  years) were included, with a mean duration ( $8.7 \pm 4.6$  years) of GH replacement before discontinuation. Of these patients, 34 aged at least 60 years (mean  $71.3 \pm 7.0$  years, range 60–88 years). The mean period of discontinuation in this group was 3.7 years (range 1–18 years); 2 years after discontinuation, 52 patients were followed, and 36 patients were followed 3 years after discontinuation. The causes for GHD were mainly of pituitary origin, with one-third of the patients having GHD due to a nonfunctioning adenoma (Table 1). A total of 43 patients (67%) received hydrocortisone replacement with a mean daily dose of  $22.6 \pm 5.7$  mg.

The main reasons for discontinuation were adverse events ( $n=25$ ) or a lack of subjective benefit ( $n=10$ ). Of the study patients, eight discontinued because of old age (12.5%), four discontinued at their own request because



**Figure 1**

Flow chart of patient selection. rhGH, recombinant human growth hormone; GH, growth hormone.

**Table 1** Baseline characteristics (*n*=64).

Age at baseline (year)	59 ± 15 (21–88)
Sex (M/F)	34/30
Cause of GHD (%)	
NFA	21 (33%)
Prolactinoma	6 (9%)
Acromegaly	10 (16%)
Cushing's disease	7 (11%)
Craniopharyngioma	4 (6%)
Other	16 (25%)
Onset (%)	
AO	55 (86%)
CO	9 (14%)
Other deficiencies ( <i>n</i> )	
Corticotrophic	43 (67%)
Thyrotrophic	45 (69%)
Gonadotrophic	46 (72%)
Diabetes insipidus	10 (16%)
Isolated GHD	2 (5%)
Duration of rhGH therapy (year)	9 ± 5 (1–18)
Cumulative dose (mg)	22.6 ± 5.7
Radiation (%)	33 (51.6%)
Medication (%)	
Antidiabetic	6.3%
Antihypertensive	43.8%
Lipid-lowering	39.1%
Oral contraceptives	1.6%
Bisphosphonates	9.4%
Calcium supplements	40.6%
Vitamin D supplements	46.9%
Thyroxine replacement	70.3%
Testosterone replacement	70.3%

AO, adult onset; CO, childhood onset; GHD, growth hormone deficiency; *n*, number of patients; NFA, nonfunctioning pituitary adenoma; rhGH, recombinant human growth hormone.

the daily injection was considered a burden (6.3%), three discontinued due to side effects (4.7%), five discontinued because they were noncompliant (7.8%), and in nine patients discontinued with no specific reason for discontinuation recorded (14.1%). IGF-1 levels decreased from  $20.1 \pm 9.9$  nmol/L (0.5 SDS) to  $9.9 \pm 2.2$  nmol/L ( $\pm 2.4$  SDS) after discontinuation.

### Literature search

The search strategy focused on discontinuation of long-term rhGH replacement, GHD adults, bone metabolism, metabolic effects, body composition, and quality of life. Only articles reporting original data were included. References of relevant articles were checked for additional articles. The search in PubMed, Web of Science, and Embase was performed on 01/06/2015 in collaboration with a trained clinical librarian, using the following search string: "Human Growth Hormone"[Majr] OR "Growth

Hormone"[ti] OR "GH"[ti] AND ("discontinuing"[ti] OR "discontinuation"[ti] OR "discontinued"[ti] OR "withdrawal"[ti] OR "withdrawing"[ti] OR "cessation"[ti] OR "deprivation"[ti]) AND ("therapy"[Subheading] OR "therapy"[ti] OR "treatment"[ti] OR "therapeutics"[Majr Terms] OR "therapeutics"[ti] OR "replacement"[ti] OR "Hormone Replacement Therapy"[Majr] OR "administration"[ti]).

Studies were eligible when all of the following criteria were met: (i) they investigated the effects of rhGH discontinuation on biochemical parameters, metabolic/anthropometric parameters, bone metabolism, QoL, muscle strength, mortality, or adverse events; (ii) had a duration of follow-up >3 months and included  $\geq 10$  patients; (iii) were performed in patients with confirmed GHD in adulthood; and (iv) were written in English language. RCTs and cohort studies were considered.

The selection of studies was done by N.M.A-D. and M.R. The two reviewers evaluated studies independently, and disagreements were resolved by consensus. Data extraction was based on data from each study provided at the population level. 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, and bone metabolism); (iv) risk of bias: the studies performed as a randomized trial, clear definitions of GHD, and duration of GH use before stopping stated, see also Appendix 1 for the used modified strobe form. Studies could qualify as very high risk of bias (0–2.5 points out of 10), high risk of bias (2.5–5 points), intermediate risk of bias (5–7.5 points), and low risk of bias (7.5–10 points). The use of statins, bisphosphonates, and glucose-lowering medication was also taken in to account.

### Statistical analysis

SPSS for Windows, version 20.0 (SPSS), was used for statistical analysis. Data are presented as mean  $\pm$  S.D., unless stated otherwise. ANOVA accounting for repeated measurements with Bonferroni correction was used to compare the parameters between baseline and *T*=1, 2, and 3 years, SPSS Bonferroni-adjusted *P*-values are given unless stated otherwise. A linear regression model was used, including age, sex, hydrocortisone use, and BMI, to identify factors influencing the metabolic effects of discontinuing GH replacement. In addition, we included the use of lipid-lowering medication, antidiabetic agents, calcium and vitamin D supplementation, and the use of

bisphosphonates in the specific analyses for bone mass, glucose metabolism, and lipid profile. Next, we also conducted a sub-analysis in elderly subjects (age >60 years,  $n=34$ ). The age of 60 years was chosen as cutoff because the effects of GH replacement therapy in GHD patients aged >60 years are not well established (16).

## Results

### Blood pressure and anthropometry

At all time points, both systolic and diastolic blood pressure did not change after discontinuation of rhGh in the whole group,  $134 \pm 10.1$  mmHg vs  $134.9 \pm 13.1$  mmHg and  $81.1 \pm 6.7$  vs  $81.2 \pm 4.9$  mmHg respectively. In

addition, there were no changes in the subgroups (<60 years and >60 years).

Fat percentage increased from  $31.5 \pm 9.5\%$  at baseline to  $33.8 \pm 9.0\%$  ( $P=0.003$ ) after 3 years. The increase was present both in patients <60 years and in those aged >60 years (from  $26.9 \pm 9.9\%$  to  $29.9 \pm 8.6\%$  ( $P=0.05$ ) and from  $34.3 \pm 8.4\%$  to  $36.1 \pm 8.7\%$  ( $P=0.001$ ) respectively). BMI decreased after discontinuation of GH therapy, which was significant after 2 years ( $P=0.014$ ), but not at 3 years  $29.2 \pm 1.1$  kg/m<sup>2</sup> vs  $28.7 \pm 1.9$  kg/m<sup>2</sup>, mean difference 0.58 (−0.28 to 1.44,  $P=0.39$ ). In patients aged <60 years, BMI decreased significantly throughout the whole study period from  $28.9 \pm 1.3$  kg/m<sup>2</sup> to  $27.9 \pm 1.83$  kg/m<sup>2</sup> (mean difference 1.12,  $P=0.04$ ) (Table 2).

**Table 2** Results after 3 years of discontinuation of rhGh per subgroup.

Parameter	Baseline	After 3 years (mmHg)	Mean difference, confidence interval	P value
Blood pressure, mmHg				
Systolic	$134 \pm 10.1$	$134.9 \pm 13.1$		
Diastolic	$81.1 \pm 6.7$	$81.2 \pm 4.9$		
<60 years				
Systolic	$128.1 \pm 10.1$	$126.3 \pm 14.6$	1.90 (−4.57 to 8.35)	0.532
Diastolic	$79.3 \pm 6.7$	$78.9 \pm 5.4$	0.41 (−5.81 to 4.98)	0.87
>60 years				
Systolic	$138.1 \pm 7.1$	$140.6 \pm 8.2$	−2.48 (−0.72 to 2.24)	0.28
Diastolic	$82.5 \pm 6.7$	$82.7 \pm 3.9$	−0.23 (−4.32 to 3.87)	0.91
BMI, kg/m <sup>2</sup>	$29.2 \pm 1.1$	$28.7 \pm 1.9$	0.58 (−0.28 to 1.44)	0.389
<60 years	$28.9 \pm 1.3$	$27.9 \pm 1.8^*$	−1.12 (0.97 to 2.14)	0.04
>60 years	$29.4 \pm 0.9$	$29.2 \pm 1.7$	0.23 (−0.59 to 1.05)	0.57
Fat mass, %	$31.5 \pm 9.5$	$33.8 \pm 9.0^*$	2.27 (−0.65 to 3.88)	0.003
<60 years	$26.9 \pm 9.9$	$29.9 \pm 8.6^*$	−3.05 (−6.07, −0.03)	0.05
>60 years	$34.3 \pm 8.4$	$36.1 \pm 8.7^*$	−1.78 (−2.75, −0.85)	0.001
Total cholesterol, mmol/L	$5.4 \pm 0.5$	$5.1 \pm 0.7$	0.27 (−0.07 to 0.60)	0.182
<60 years	$5.4 \pm 0.5$	$5.2 \pm 0.7$	0.16 (−0.17 to 0.48)	0.32
>60 years	$5.4 \pm 0.5$	$5.0 \pm 0.7$	0.34 (−0.16 to 0.70)	0.06
LDL-cholesterol, mmol/L	$3.2 \pm 0.4$	$2.9 \pm 0.6$	0.29 (−0.031 to 0.6)	0.097
<60 years	$3.2 \pm 0.5$	$3.0 \pm 0.5$	0.21 (−0.08 to 0.51)	0.14
>60 years	$3.2 \pm 0.4$	$2.8 \pm 0.6^*$	0.33 (−0.68 to 0.02)	0.061
HDL-cholesterol, mmol/L	$1.4 \pm 0.2$	$1.5 \pm 0.2$	−0.05 (−0.16 to 0.06)	1.00
<60 years	$1.4 \pm 0.2$	$1.5 \pm 0.3^*$	0.20 (−0.01 to 0.30)	0.043
>60 years	$1.5 \pm 0.2$	$1.5 \pm 0.2$	0.20 (−0.04 to 0.09)	0.485
Glucose, mmol/L	$5.0 \pm 0.5$	$5.4 \pm 1.7$	−0.36 (−1.09 to 0.37)	1.00
<60 years	$4.8 \pm 0.4$	$5.3 \pm 1.2$	−0.57 (−1.27 to 0.14)	0.11
>60 years	$5.1 \pm 0.6$	$5.3 \pm 2.0$	−0.23 (−1.02 to 0.57)	0.554
Lumbar spine BMD, g/cm <sup>2</sup>	$1.05 \pm 0.09$	$1.05 \pm 0.14$	−0.00 (−0.06 to 0.06)	1.00
<60 years	$1.105 \pm 0.05$	$1.02 \pm 0.13$	0.03 (−0.05 to 0.11)	0.41
>60 years	$1.09 \pm 0.09$	$1.14 \pm 0.09$	−0.05 (−0.11 to 0.02)	0.12
Femoral neck BMD, g/cm <sup>2</sup>	$0.82 \pm 0.12$	$0.78 \pm 0.12$	0.05 (0.00 to 0.09)	0.061
<60 years	$0.92 \pm 0.08$	$0.85 \pm 0.1^*$	0.07 (0.04 to 0.11)	0.001
>60 years	$0.77 \pm 0.10$	$0.77 \pm 0.09$	0.00 (−0.06 to 0.07)	0.91
P1NP, ng/mL	$42.0 \pm 9.1$	$32.5 \pm 9.9^{a*}$	6.90 (4.99 to 8.81)	<0.001
Beta crosslaps, ng/mL	$0.41 \pm 0.06$	$0.31 \pm 0.07^{a*}$	0.10 (0.10 to 0.12)	<0.001

BMD, bone mineral density; P1NP, total procollagen type 1 N-terminal propeptide.

aValue after 1 year. \*Significant change from baseline.



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## Lipids and glucose

After 3 years of discontinuation, serum total cholesterol and LDL-cholesterol (TC) levels were decreased from  $5.4 \pm 0.5$  mmol/L to  $5.1 \pm 0.7$  mmol/L ( $P=0.182$ ) and from  $3.2 \pm 0.4$  mmol/L to  $2.9 \pm 0.6$  mmol/L ( $P=0.097$ ). HDL-C increased after 3 years,  $1.4 \pm 0.2$  mmol/L to  $1.5 \pm 0.2$  mmol/L. In the subgroup analyses in patients aged <60 years, this increase was significant ( $P=0.04$ ). The percentage of patients on lipid-lowering agents, predominantly statins, was 39 at baseline and 44 at the end of follow-up, exclusion of these patients did not alter the outcome. Plasma glucose concentration did not change after discontinuation,  $5.0 \pm 0.5$  mmol/L vs  $5.4 \pm 1.7$  mmol/L, nor did the number of patients on glucose-lowering therapy,  $n=4$  (6.3%) at baseline. Subgroup analyses between patients <60 years and >60 years did not reveal differences (Table 2).

## Bone metabolism

Lumbar spine BMD remained stable ( $1.05 \pm 0.09$  g/cm<sup>2</sup> vs  $1.05 \pm 0.14$  g/cm<sup>2</sup>) with no age-related differences. Femoral neck BMD ( $0.82 \pm 0.12$  g/cm<sup>2</sup> vs  $0.78 \pm 0.12$  g/cm<sup>2</sup>) in the whole group did not change (mean difference 0.05,  $P=0.061$ ). However, in the subgroup of patients <60 years, BMD decreased from  $0.92 \pm 0.08$  g/cm<sup>2</sup> to  $0.85 \pm 0.1$  g/cm<sup>2</sup> after 3 years ( $P=0.001$ ) (Table 2). *T*-scores of the whole cohort at the lumbar spine were  $-0.35$  at baseline and changed to  $-0.38$  at 3 years (mean difference  $-0.02$ ,  $P=0.83$ ). In the femoral neck, the *T*-score dropped from  $-0.92$  at baseline to  $-1.08$  after 3 years (mean difference  $-0.158$ ,  $P=0.040$ ). In the whole cohort, osteoporosis was present at baseline in three patients and osteopenia in 19 patients. After 3 years, not a single patient had BMD in the osteoporotic range and 17 had osteopenia. Bisphosphonate use increased from 9.4% at baseline to 12.1% after 3 years. In all patients, a clinical assessment was performed during the follow-up, including a radiological assessment, when indicated. At baseline, 19 patients suffered from a fracture (one hip fracture, three vertebral fractures, and 13 non-hip, non-vertebral fractures).

During the follow-up, only three fractures occurred (one in the group aged <60 years).

Bone turnover markers P1NP and beta crosslaps decreased 1 year after discontinuation of therapy in the whole group: P1NP from  $42.0 \pm 9.1$  ng/mL to  $32.5 \pm 9.9$  ng/mL ( $P<0.001$ ), beta crosslaps from  $0.41 \pm 0.06$  ng/mL to  $0.31 \pm 0.07$  ng/mL, mean difference 6.90,  $P<0.001$  (Table 2). Subgroup analyses showed the same patterns.

Markers for bone turnover were available in a small subgroup both at baseline and after 3 years. P1NP decreased from  $42.2 \pm 8.8$  ng/mL to  $37 \pm 13.7$  ng/mL and beta crosslaps decreased from  $0.41 \pm 0.06$  ng/mL to  $0.36 \pm 0.16$  ng/mL; however, these changes were not significant and group sizes were small.

## Systematic review

The initial search resulted in a total of 95 articles (Table 3). Of these, 26 publications were retrieved for full assessment, 17 papers were excluded as they reported on patients <18 years, one because of duration of follow-up of only 5 days, and one because of a low number of patients. Also, eight articles (that included a total number of 166 patients) met the inclusion criteria, three were RCTs and five were cohort studies. The number of included patients per study ranged from 10 to 42.

## Study characteristics

Details of the included studies are summarized in Table 3. Included studies were published between 1992 and 2012. Of the included studies, three ( $n=61$  patients in total) were randomized controlled trials, all had a crossover design. The mean duration of withdrawal was 3–18 months in all studies except one. Two studies did not clearly report the duration of rhGh replacement at the time of discontinuation; in the other studies, the duration of rhGh treatment before termination ranged from 6 months to 10 years (27, 30).

Three studies qualified as having a low risk of bias (30, 31, 32), all were RCTs, and the remaining studies were qualified as having an intermediate risk of bias. None of the studies mention 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.

## Anthropometry and body composition (three studies)

Body composition was measured in three studies, and all reported an increase in fat mass and decrease in lean body mass after a follow-up of 3–18 months (28, 30, 31). One study reported on BMI and waist and hip circumference: no statistically significant changes were observed 6 months after discontinuation (31).

**Table 3** Results of the systematic review.

Reference	Study design of Bias ass. Nr points/10	Time (months)	N% M/F	Age years	Duration of replace- ment at baseline (years)	Bone metabolism	Body composition	Glucose metabolism	Cholesterol metabolism	Other reported effects
(30)	RCT, crossover 8.5/10	18	20100/0	48.9±2	NR Time between baseline and diagnosis is 7 years	Increase of hip BMD: +0.0014±0.0042 g/cm <sup>2</sup> (P 0.0051) Stable BMD of the spine: +0.0018±0.00097 g/cm <sup>2</sup> (P 0.087) BMC did not change	LBM decreased: 2133 gram±539 g (P 0.0016) Fat mass increased: 3.18±0.44% (P 0.0001)	NR	NR	NR
(29)	Cohort study 6.5/10	6	1744/56	39 (25–50)	6 months during trial	NR	NR	NR	TG increased: 19.9 mg/dL (P 0.007) HDL decrease: 2.4 mg/dL (P 0.004) hsCRP increase (mg/L): 3.4±0.7 to 6.2±1.6 (P 0.0001)	Diastolic blood pressure increase: 76.7±3.8 to 80.0±6.1 (P 0.0007)
(31)	RCT, crossover 8.5/10	4	2968/32	60 (28–73)	10.1±3.4 (3–16)	BMC increased: 0.002±0.11 g/cm (CI 0.004–0.006) P 0.0047	Fat mass increased: 2.05±2.32 kg (CI 1.45–2.56) (P<0.001) BMI and WH circumfer- ence: no change	Glucose levels stable: −0.36±1.62 (CI −0.53 to 0.18) HbA1c (%) decreased: −0.18±0.42 (CI 0.30– 0.07) (P 0.02)	TC increase (mmol/L): 0.2 (P<0.05) HDL increased (mmol/L): 0.05 (P<0.05) LDL increase (mmol/L): 0.3 (P<0.01) TG decrease (mmol/L): −0.2CRP increase (mg/L): 1.3 (P<0.05)	AGHDA scores worsened, NHP/ PGWB subscores on emotional and positive well- being worsened (P<0.05)
(27)	Cohort study 5.5/10	0–252	4252/48	19 (14–38)	NR	NR	NR	NR	Hypertriglyceride- mia 41%, NAFLD 29%, HC 26%, DM 10%	NR
(44)	Cohort study 6.5/10	12	2070/30	40.2 (22–56)	18–24 months	Stable BMD in L2– L4 +0.008 g/cm <sup>2</sup> femoral neck no change	NR	NR	NR	NR
(43)	Cohort study 6/10	12	1080/20	20.4±2.2	12 months	Forearm cortical BMC increased: 1.48±0.04 vs 1.44±0.05 g/cm <sup>2</sup> . No change in forearm integral BMC or in vertebral trabecular BMD	NR	NR	NR	NR

(Continued)

Table 3 (Continued).

Reference	Study design Nr points/10	Time (months)	N% M/F	Age years	Duration of replace- ment at baseline (years)	Bone metabolism	Body composition	Glucose metabolism	Cholesterol metabolism	Other reported effects
(32)	RCT7.5/10	3	1250/50	44.9(25–68)	5	NR	NR	NR	NR	QoL questionnaires (SF-36, GWB, HBQoL) decrease in energy, tiredness. More profound in younger male participants, almost no complaints in subgroup >53 years
(28)	Cohort study 6/10	6	1650/50	49(31–60)	1	NR	Decrease LBM, increase fat mass	Glucose remained stable	Increase in CRP	

BMD, bone mineral density; BMC, bone mineral content; LBM, lean body mass; RCT, randomized controlled trial; WH circumference, waist hip circumference; GHD, growth hormone deficiency; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; rhGH, recombinant human growth hormone; QoL, quality of life.

### Lipid metabolism (four studies)

Total cholesterol and LDL-C increased in three studies but did not change in another study (27, 29, 31). An increase in hsCRP after discontinuation of rhGh therapy has been reported in two studies (28, 29).

### Glucose metabolism (two studies)

Fasting glucose remained stable in both studies; however, HBA1c was lower in one study after discontinuation of rhGh (28, 31).

### Bone metabolism (three studies)

Several parameters were reported: one study found an increase in BMC during the study period, whereas a second study did not report any difference in BMC (30, 31). The studies had a duration of follow-up of 6, 12, and 18 months, respectively, and reported a stable or increase in BMD at the hip and spine (30, 31, 43). None reported on fracture prevalence or bone markers.

### Quality of life (two studies)

Two studies reported on quality of life (31, 32). After discontinuation of rhGh replacement for a period of 3–4 months, patients reported worsened scores on emotional reactions and well-being. Furthermore, they reported an increase in tiredness. Noteworthy, these effects were more profound in younger male participants and almost absent in older patients (32).

### Discussion

In this study, we demonstrated that GHD patients who discontinued rhGh replacement for various reasons did not show obvious adverse metabolic changes in the long term, besides an increase in fat mass and a significant decrease in bone turnover markers during the first year after discontinuation. When the results, however, were stratified for age (< or >60 years), small but significant changes were also observed in BMI, HDL-C, and femoral neck BMD only in patients <60 years. This implicates that advanced age is a factor that should be taken into account when (dis)continuation of rhGh replacement is considered both on clinical grounds and for clinical trials. The decrease in femoral neck BMD in patients <60 years was not accompanied by an increase in fracture



rate, although patient numbers were too small to detect a difference in fracture incidence.

It appears that rhGH replacement can be discontinued under certain clinical circumstances such as older age, provided that routine cardiovascular clinical guidelines for the treatment of lipid abnormalities and hypertension are followed, especially in patients >60 years. At all time points, lipid and fasting glucose concentrations remained within the normal range in both age groups, and BMI even decreased after discontinuation of rhGH in the group <60 years. In the general population, for every 1 mmol/L LDL-C reduction, the risk of major vascular events decreases by 20% (34). Because the adverse lipid profile in adult GHD patients is associated with increased cardiovascular risk, it might be beneficial to start lipid-lowering medication in all middle-aged GHD patients, in addition to rhGH replacement. The clinical implications of the average 0.4 mmol/L increase in fasting glucose levels after discontinuation are not clear as fasting glucose levels remained within the normal range at all time points. Previous epidemiological studies have shown that the hazard ratio for coronary heart disease does not differ among patients with fasting glucose concentrations ranging between 3.9 and 5.6 mmol/L and that the incidence of coronary heart disease increases with increasing BMI (35, 36). On average, all patients would be classified as overweight at all time points; however, as BMI might not be the best anthropometric predictor for cardiovascular events, the observed increase in fat percentage might counteract the decrease in BMI after discontinuation (37). The decline in BMI with a rise in fat mass could be very well explained by a decrease in lean body mass, as reported in other discontinuation studies (30, 31, 39). Unfortunately, we were not able to collect data on LBM in all our patients, and therefore, we were not able to evaluate this item in this study.

Treatment of adult GHD is mainly indicated for improvement of cardiovascular risk factors and quality of life. Short- and long-term studies have demonstrated that GH replacement is associated with improvement of cardiovascular risk factors such as lipid profile, bone mass, and quality of life (5, 7, 9, 20, 33). However, data also show that the metabolic phenotype of GHD patients remains abnormal compared with the general population despite long-term replacement. Therefore, it is very well possible that the classic GHD phenotype is not be completely attributable to growth hormone deficiency and/or that not all effects are reversible by current rhGH replacement strategies (11, 12).

This study has strengths as well as limitations, being an observational study reporting on the results of a large, well-characterized cohort with a long duration of follow-up. There are no guidelines for discontinuation of rhGH replacement; consequently, the observed group was clearly pre-selected by the treating physician. Also in this study, we did not systematically evaluate the effects on quality of life, another important indication for GH replacement, by the use of pre-specified questionnaires. However, it is plausible that in case of perceived subjective deterioration, rhGH would have been re-initiated, as was reflected by the ten patients that were identified before inclusion that re-initiated treatment within the first year. A clear strength of this study is the long follow-up after discontinuation and the evaluation of not only bone mass density but markers of bone turnover as well. Although the data on bone turnover markers are limited in our study, this finding could be of clinical relevance in the future. GH and IGF-1 are important anabolic hormones. Most of the effects of GH are mediated by systemic and/or local IGF-1, enhancing the differentiated function of osteoblasts and bone formation, although GH may also act directly on bone cells. Untreated GHD in adults is characterized by low bone turnover and decreased BMD and BMC. RhGH replacement therapy increases overall bone turnover, with the main effect on the lumbar spine. After discontinuation of rhGH, there seems to be a gradual decline in bone resorption as well as formation, leading to stabilization of the bone mass. In this way, one can explain the observed stabilization of bone mass, not only in our study but in the literature as well.

In order to put our observations in the best perspective, we additionally performed a systematic literature search on studies reporting on discontinuation of GH replacement in adults. A total of 144 patients were reported, of whom 84 were included in randomized controlled studies. The duration of follow-up was limited and ranged between 3 and 18 months. Overall, most studies reported that a parameter did not change without mentioning the raw data. This makes it hard to interpret these literature results, as this implies that there was no change at all, whereas the study can only report that there is no evidence of a difference in their small patient group (38). The majority of included patients had been on rhGH replacement for only 6–12 months before discontinuation, and some studies did not even report the duration of therapy. This precludes a definite and firm interpretation of the results, as the effects of rhGH are time dependent. For instance, a decrease in BMD might be observed within the first

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year affecting the effects of withdrawal when this occurs within the first year (7, 9, 19). Nevertheless, all studies reporting on body composition, including this study, have consistently shown an increase in fat percentage after discontinuation (21, 28, 31). The effects on lipids were not conclusive after discontinuation, also because data on the use of lipid-lowering medication could not be extracted, or subjects on lipid-lowering agents were excluded. Biller *et al.* reported an ongoing increase in BMD after 18 months of discontinuation, although data on bone-modifying agents including calcium and vitamin D were not available (30). One study reported on patients ( $n=29$ ) who used rhGh during a longer period of time (31). In the 4-month follow-up period in this study, BMC and fat mass increased, whereas lipid profile and quality-of-life scores, however, worsened, and glucose levels remained grossly unchanged. The study did not provide information on the use of statins or bisphosphonates. Finally, a potential effect of age, as we have demonstrated in this study, could not be extracted.

There is a clear rationale for a restrictive approach toward rhGH replacement in the elderly. There is physiological decline in the activity of the GH/IGF-1 axis with aging, improving longevity as functional mutations of the IGF-1R gene resulting in altered IGF-1 signaling appear to be more common in centenarians than in younger controls (40). Mice lacking GHR live longer, and increasing IGF1 levels in these mice reverted their longevity to the level of non-mutant mice (41, 42). Additionally, the GH/IGF-1 axis has been linked with cancer (45, 46). Despite the clear age-related decline in IGF-1 levels, there is insufficient awareness of the necessity of reducing the rhGh replacement dose with advancing age, and age-adjusted reference values (especially for those >65 years) are not routinely available. However, such an optimization of the activity of the GH/IGF-1 axis requires a greater understanding of the array of interactions between GH, IGF-1, and tissue specificity.

In conclusion, the results of this study indicate that discontinuation of rhGh replacement in routine clinical practice does not result in apparent negative effects on overall metabolic profile in elderly patients, whereas this seems less clear for patients younger than 60 years. As long-term replacement with rhGh will generally not normalize the metabolic profile and the beneficial effects of unrestricted GH replacement therapy especially in elderly GHD are yet inconclusive, we advise to critically reevaluate the need for lifelong rhGh treatment in adult GHD patients and to explore alternative treatment

strategies in patients, such as a more stringent treatment of dyslipidemia and hypertension, especially in the elderly patients. Further studies need to be performed to determine optimal strategies to withdraw rhGH in aging GHD patients. Finally, it is important to accentuate that future trials evaluating the effects of discontinuing rhGh replacement in the long-term should include evaluation of QoL, patient preferences, and costs.

#### 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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