

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/33195> holds various files of this Leiden University dissertation.

**Author:** Appelman-Dijkstra, Natasha Mireille

**Title:** Long-term consequences of growth hormone replacement and cranial radiation on pituitary function

**Issue Date:** 2015-06-04

---

# Chapter 8

**Discontinuing recombinant growth hormone replacement  
in adult GH deficient patients: a cohort study and  
systematic review of literature.**

---

Natasha M. Appelman-Dijkstra, Marnick Rijndorp, Nienke R. Biermasz,  
Olaf M. Dekkers, Alberto M. Pereira

*Submitted*

### ABSTRACT

*Background:* Growth hormone (GH) replacement is advocated in adult Growth hormone deficient (GHD) patients to increase bone mass, to improve lipid profile and body composition, and Quality of Life. However, data on the consequences of discontinuation of GH replacement are scarce in adult GHD patients.

*Design:* Cohort study and a systematic literature search aimed at the evaluation of the metabolic effects of GH discontinuation on anthropometry, glucose and lipid metabolism, and bone mass in adult GHD patients.

*Methods:* We included 64 adult GHD patients who discontinued GH replacement for > 12 months after a duration of rhGH replacement of  $8.7 \text{ years} \pm 4.6 \text{ years}$ . AGE range! Data on anthropometry, lipids, glucose, and bone mass were assessed until 3 years after discontinuation of therapy. In addition, a systematic literature review was performed using the electronic databases Pubmed, Embase, and Web of Science.

*Results:* Fat mass increased from  $31.5 \pm 9.5\%$  to  $33.8 \pm 9.0\%$  ( $p < 0.001$ ) after 3 years of discontinuation. Total - and LDL-cholesterol levels decreased from  $5.4 \pm 0.5 \text{ mmol/L}$  to  $5.1 \pm 0.7 \text{ mmol/L}$  ( $p = 0.03$ ), and  $3.2 \pm 0.4 \text{ mmol/L}$  to  $2.9 \pm 0.6 \text{ mmol/L}$  ( $p = 0.016$ ) after discontinuation in the presence of an increase in the use of lipid lowering medication. Fasting glucose levels and bone mass did not change. In patients aged > 60 years ( $n = 34$ ) no significant changes were observed in any of the studied parameters. These observations, except for the changes in lipid profile, were in line with the results of the systematic review, which included 7 studies with a maximum duration of follow up of 18 months.

*Conclusions:* We did not observe obvious adverse metabolic changes in the 3 yrs following discontinuation of GH replacement for various reasons in adult patients with GHD. Further research is needed to determine optimal strategies for long-term GH replacement including the optimum time point for GH discontinuation.

## **INTRODUCTION**

Adult GHD is associated with an adverse metabolic profile, including abdominal obesity, dyslipidemia and an increased cardiovascular risk and mortality (1,2). Several studies have demonstrated that GHD patients have lower bone mass, increased fracture risk, and an impaired quality of life (QoL) (3,4). Recombinant human growth hormone (rhGH) replacement therapy has shown to improve lipid profile, body composition, quality of life, and to increase bone mass, and has become available for adult patients with GHD since 2 decades (5-10). However, long-term follow up studies have shown that the prevalence of the metabolic syndrome does not ameliorate and BMI increases while on rhGH replacement. In addition, the metabolic profile of long-term treated GHD patients remains significantly different from the general population (8, 11,12).

At present, many issues regarding long-term treatment are not well established, for example the optimal duration of rhGH replacement with advancing age, the long-term efficacy and the consequences of rhGH withdrawal in adulthood are not well established. Therefore, replacement is continued indefinitely in many cases. However, in case of an active malignancy or lack of subjective benefit it is advised to stop rhGH replacement. In addition, there are anecdotal data questioning the beneficial effects of rhGH replacement with advancing age, since 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 man (13,14). In addition, studies reporting on the efficacy of rhGH replacement in elderly GHD patients are limited and show inconclusive results, and data on rhGH discontinuation in adult GHD are scarce (15). Therefore, we aimed to evaluate the long-term 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 and reasons for discontinuation of rhGH in case of lack of subjective benefit, malignancy, side effects, and at older age.

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

## **PATIENTS AND METHODS**

### **Patients**

Patients were identified from the database of our cohort of adult patients with GHD. This cohort comprised all patients starting rhGH since 1994, with standardized evaluation of clinical and metabolic parameters annually at the outpatient clinic of the Center for Endocrine Tumors (8, 11,12, 16-18). For the present analyses, we included all GHD patients treated continuously for at least 12 months with rhGH during adulthood, and who discontinued rhGH replacement therapy for at least for 12 months for various

reasons. Patients with a baseline visit before discontinuation and at least one follow up visit after discontinuation were included.

### **Treatment protocol**

Severe GHD was documented prior to start of rhGH replacement and defined as a GH peak response to the Insulin Tolerance Test (ITT)  $<3\mu\text{g/l}$  (glucose nadir  $<2.2\text{mmol/l}$ ) according to current guidelines, or, in case of contraindications for ITT, by combined Growth Hormone Releasing Hormone/Arginine-stimulation (GHRH/Arg) with BMI-adjusted GH cut-offs, (19-24). According to protocol patients receiving rhGH replacement during childhood were retested at the time of transition to the adult outpatient clinic, after treatment cessation for at least 3 months. Hormone deficiencies were diagnosed and treated as previously reported (8,25). Patients were treated with bisphosphonates, calcium and vitamin D replacement, lipid-lowering and antihypertensive medication according to the discretion of their attending physicians, in accordance with national guidelines, which was continued after withdrawal of rhGH replacement. Efficacy and safety parameters were assessed yearly, next to a routine assessment of pituitary function.

## **STUDY DESIGN AND METHODS**

### **A) Cohort Study**

We performed a cohort study, aimed at evaluation of the metabolic effects of rhGH discontinuation. The baseline visit was defined as the last visit prior to discontinuation of rhGH replacement. Data were assessed at baseline, and at 1, 2, and 3 years after stop.

During the periodical visits, the following data were assessed:

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 ( $\text{kg/m}^2$ ).
2. Biochemical parameters: serum concentrations of IGF-1, GH, TSH,  $\text{fT}_4$ , LH, FSH, estradiol, testosterone, prolactin, bone turnover markers, PTH, vitamin D, glucose, parameters for renal and kidney function, 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 Bodycomposition: Data on BMD, BMC and fatpercentage were collected. BMD was measured yearly 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) (25). Fatpercentage was assessed by calculating the total mass of fat divided by total body mass.

4. Data on medication use and co-morbidity was obtained from electronic patient files.

## **B) Literature search**

We composed a search strategy focusing on discontinuation of long-term rhGH treatment, GHD adults, bone metabolism, Quality of life, metabolic effects, and body composition. Only articles reporting original data were included, studies reporting duplication of cohorts were excluded. References of relevant articles were checked for additional articles. The search in Pubmed, Web of Science, and Embase was performed on 05/09/2014 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: (1) they investigated effects on biochemical, metabolic/anthropometric parameters, bone metabolism, QoL, muscle strength, mortality, or adverse events, (2) had a duration of follow up > 1 month and included > 10 patients, (3) were performed in patients with confirmed GHD in adulthood, and (4) were written in English.

The selection of studies was done by two reviewers (N.M.A-D.en 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: (1) study population (patient characteristics, population size, GHD assessment, control population); (2) exposure to rhGH (duration of rhGH treatment, rhGH dose), (3) outcome (biochemical and anthropometric parameters, QoL, bone metabolism) (4) risk of bias.

## **STATISTICAL ANALYSIS**

SPSS for Windows, version 20.0 (SPSS, Inc.) was used for statistical analysis. Data are presented as mean  $\pm$  SD, unless stated otherwise. ANOVA accounting for repeated measurements with Bonferroni correction was used to compare 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, radiotherapy, hydrocortisone use, BMI, to identify factors influencing the metabolic effects of discontinuing rhGH replacement therapy. In addition, we included the use

of antihypertensive medication, use of lipid-lowering medication, anti-diabetic agents, calcium and vitamin D supplementation, and the use of bisphosphonates. We also conducted a sub-analysis in elderly subjects (age >60, n=34). The age of 60 was chosen as cut-off, because the effects of GH replacement therapy in GHD patients aged >60 years is not well established (15).

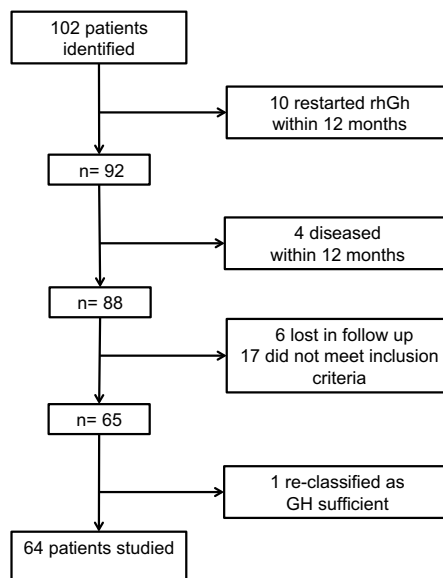
## RESULTS

### Clinical characteristics

A total of 102 patients who discontinued therapy were identified. Of these, 4 patients died before the first annual visit after cessation of rhGH replacement, 10 patients re-initiated rhGH replacement within one year, 6 patients were lost to follow up, and 18 patients did not meet the inclusion criteria. See *Figure 1* for flow-chart of patient inclusion.

A total of 64 patients, mean age  $59.7 \pm 15.7$  years, were included in the study. Duration of rhGH replacement was  $8.7 \text{ years} \pm 4.6$  years. Thirty-four patients (53% of total) were 60 years or older. Mean age in the subgroup of elderly patients was  $71.3 \pm 7.0$  years. Mean period of discontinuation was 3.7 years (range 1-18 years). The main reasons for discontinuation were adverse events (n=25), or a lack of subjective benefit (n=10).

*Table 1*



**FIGURE 1.**

Flow chart patient selection

rhGH; recombinant human growth hormone, GH ; growth hormone

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

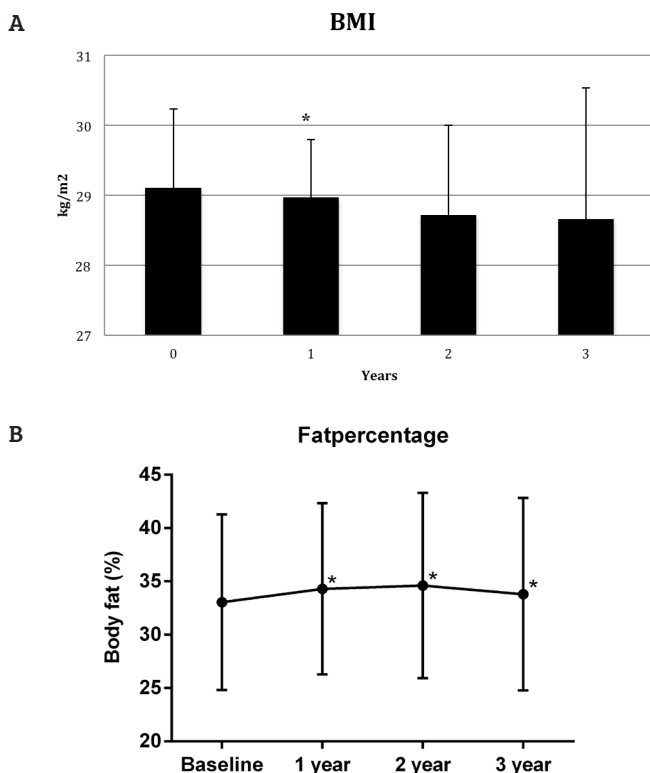
Age at baseline (yr)	59 ±15 (21-88)
Sex (M/F)	34/30
<b>Cause of GHD (%)</b>	
NFA	21 (33%)
Prolactinoma	6 (9%)
Acromegaly	10 (16%)
Cushing's disease	7 (11%)
Craniopharyngioma	4 (6%)
Other	16 (25%)
<b>Onset (%)</b>	
AO	55 (86%)
CO	9 (14%)
<b>Other deficiencies (n)</b>	
Corticotropic	43 (67%)
Thyreotropic	45 (69%)
Gonadotropic	46 (72%)
Diabetes insipidus	10 (16%)
Isolated GHD	2 (5%)
Rh-GH duration (yr)	9 ± 5 (1-18)
Cumulative Dose (mg)	22.6 ± 5,7
Radiation (%)	33 (51.6%)
<b>Medication (%)</b>	
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%
Dosage (µg)	118.7 ± 41.4

AO = adult onset, CO = childhood onset, GHD = Growth hormone deficiency, n = number of patients, NFA = non-functioning pituitary adenoma, rhGH = recombinant human growth hormone, yr = years.

## Anthropometry and blood pressure

Both systolic and diastolic blood pressure did not change significantly after discontinuation of growth hormone replacement therapy,  $134 \pm 10.1$  mmHg *vs*  $134.9 \pm 13.1$  mmHg and  $81.1 \pm 6.7$  *vs*  $81.2 \pm 4.9$  mmHg respectively.

BMI decreased in the first years after cessation of rhGH therapy (*Figure 2 A & B*). In elderly subjects, BMI did not significantly decrease, mean difference  $0.8$  kg/m<sup>2</sup>, 95% CI  $-0.3$ -  $1.8$ . Fat percentage increased from  $31.5 \pm 9.5$  % to  $33.8 \pm 9.0$  % ( $p < 0.001$ ) after 3 years. Subgroup analyses in patients  $> 60$  years of age did not show any significant change in fat percentage after 3 year, mean difference  $-0.6\%$  with 95%CI  $-2.3$ -  $1.0$ .



**FIGURE 2A&B.** Changes in BMI up to 3 years after discontinuation.

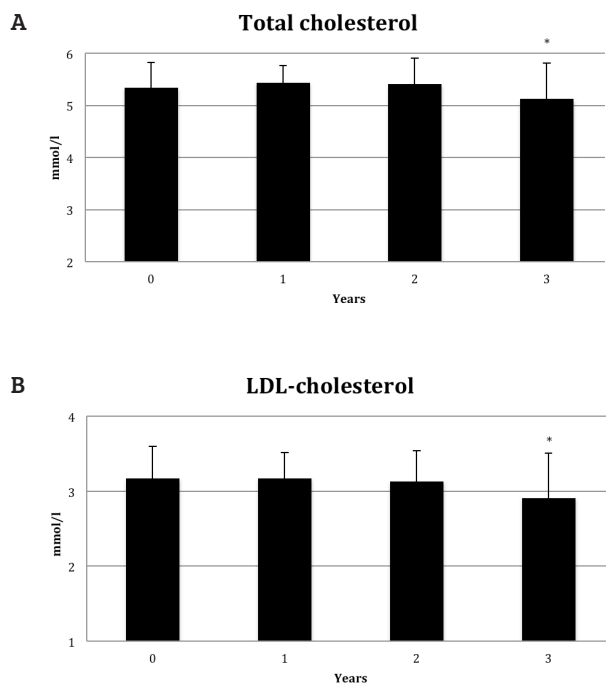
BMI: Body Mass Index kg/m<sup>2</sup>; \* $p < 0,05$  compared to baseline

## Lipid and glucose profile *Figure 3A & B*.

After 3 years of discontinuation serum total- and LDL-cholesterol (TC), decreased significantly from  $5.4 \pm 0.5$  mmol/L to  $5.1 \pm 0.7$  mmol/L ( $p = 0.03$ ), and from  $3.2 \pm 0.4$  mmol/L to  $2.9 \pm 0.6$  mmol/L ( $p = 0.016$ ). HDL-C concentration after 3 years did not change,  $1.4 \pm 0.2$  *vs*  $1.5 \pm 0.2$  mmol/L.

The percentage of patients on lipid lowering agents, predominantly statins, was 39 %at baseline and increased during follow up to 44%.

Glucose concentration and the number of patients on glucose lowering therapy did not change after discontinuation,  $4.9\pm 0.5$  mmol/L vs  $5.4\pm 1.7$  mmol/L. In the elderly patients, no changes were observed.



**FIGURE 3A&B.** Changes in total and LDL cholesterol levels up to 3 years after discontinuation

\* =  $P < 0.05$  compared to baseline

### **Bone metabolism**

Lumbar spine BMD and femoral neck BMD remained stable,  $1.0\pm 0.1$  g/cm<sup>2</sup> vs  $1.1\pm 0.2$  g/cm<sup>2</sup> and  $0.8\pm 0.1$  g/cm<sup>2</sup> vs  $0.8\pm 0.1$  g/cm<sup>2</sup> respectively. Bisphosphonate use increased from 9.4% at baseline to 12.1% after 3 years. In a small subgroup (n=17) bone markers were available at baseline and after 3 years. P1NP decreased from  $42.2 \pm 8.8$  ng/mL to  $37 \pm 13.7$  ng/mL ( $p=0.064$ ). Beta crosslaps decreased from  $0.41 \pm 0.06$  ng/mL to  $0.36\pm 0.16$  ng/mL ( $p= 0.056$ ).

### **SYSTEMATIC REVIEW**

The initial search resulted in a total of 95 articles. Of these, 26 publications were retrieved for full assessment, 17 papers were excluded since they reported on patients

< 18 years, 1 because of duration of follow up of only 5 days and 1 because of a low number of patients. Seven articles (that included a total number of 166 patients) met the inclusion criteria. The number of included patients per study ranged from 10 to 42.

*Table 2*

### **Study characteristics**

Details of the included studies are summarized in Table 2. Included studies were published between 1992 and 2012. Six studies (n= 90 patients in total) were randomized controlled trials, of which 3 had a crossover design, there was one retrospective cohort study. The mean duration of withdrawal was 3-18 months in all studies except one. This was a cohort study including 42 patients with duration of follow up between 0-21 Years (26). Two out of 7 studies did not clearly report the duration of rhGH therapy at time of discontinuation (26,29). Overall quality of the studies was fair with a low risk of bias since there were designed as RCT, although none of the studies mention handling of statins, bisphosphonates and glucose lowering medication or even excluded patients on these medications. In addition data reported in the studies are heterogeneous and therefore precluded a formal meta-analyses.

### **Anthropometry and Body composition:**

One study reported on BMI, waist and hip circumference: no statistically significant changes were observed after 6 months of follow up (30). 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 (27,29,30).

### **Lipid metabolism:**

Total Cholesterol and LDL increased in 3 studies but was did not change in another study (26,28,30). Two studies also reported an increase of hsCRP after discontinuation of rhGH therapy (27,28)

### **Glucose metabolism:**

Two studies reported on glucose metabolism and insulin sensitivity after discontinuation (27,30). Fasting glucose, insulin levels, c-peptide and HBA1c were lower in 2, however one study reported an increase of glucose levels.

**TABLE 2.**

Author	Study Design	Time (months)	N (%)	Age (years)	Duration of replacement at baseline (years)	Bone Metabolism	Body Composition	Glucose Metabolism	Cholesterol Metabolism	Other reported effects
Billir	RCT, crossover	18	20 (100/0) M/F	48.9 ± 2	NR Time between baseline and diagnosis is 7 yrs	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 gram (p 0.0016) Fat mass increased: 3.18% ± 0.44% (p 0.0001)	NR	NR	NR
Colao	RCT, crossover	6	17 (44/56) M/F	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.004) increase hsCRP (mg/liter): 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)
Filippson	RCT, crossover	4	29 (68/32) M/F	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 kg ± 2.32 (CI 1.45-2.56) (p < 0.001)	Glucose levels stable -0.36 ± 1.62 (CI -0.53-0.18) HbA1c (%) decreased -0.18 ± 0.42 (CI 0.30 -0.07) (p 0.02)	TC mmol/l increase: 0.2 (p < 0.05) HDL mmol/l increased 0.05 (p < 0.05) LDL mmol/l increase 0.3 (p < 0.01) TG mmol/l decrease -0.2 (p < 0.05)	AGHDA scores worsened, NHP/PQWB subscores on emotional and positive well being worsened (p < 0.05)

Author	Study Design	Time (months)	N (%)	Age (years)	Duration of replacement at baseline (years)	Bone Metabolism	Body Composition	Glucose Metabolism	Cholesterol Metabolism	Other reported effects
Fukuda	Retrospective	0-252	42 52/48	19 (14-38)	NR	NR	NR	NR	TC increased as well as triglycerides	NR
Gomez	Observational crossover	12	20 70/30	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
Holmes	Observational crossover	12	10 80/20	20.4 ±2.2	12 months	forearm cortical BMC increase 0.1 g/cm (p 0.00) vertebral trabecular BMD 0.0063 g/cm <sup>2</sup> NS	NR	NR	NR	NR
Mc Millan	RCT	3	12 50/50	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
Yuen	RCT	6	16 50/50	49 (31-60)	1	NR	Decrease LBM, increase Fat mass,	glucose remained stable	increase in CRP	

\* median; BMD: Bone Mineral Density, BMC :Bone Mineral Content, LBM: Lean Body Mass, RCT: Randomized Controlled Trial, WH circumference: waist hip circumference. GHID: Growth Hormone Deficient, TC: Total Cholesterol, LDL-C: LDL- cholesterol, HDL-C: HDL- Cholesterol, rhGH: recombinant human Growth Hormone, QoL: Quality of Life.

### **Bone metabolism:**

Several parameters were reported. One study found an increase in BMC during the study period where a second study did not report any difference in BMC (29,30). Two studies with a duration of follow up of 6 months and 18 months respectively, reported a stable or increase of BMD at the hip and spine (29,30). No study reported on fracture prevalence or bone markers.

### **Quality of Life:**

Only 2 studies reported on quality of life (30,31). After discontinuation of rhGH 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 (31).

In conclusion most studies investigated the effects of growth hormone discontinuation in the follow up course after short-term rhGH supplementation. Only 2 studies reported on patients treated for more than 5 years of rhGH supplementation and their follow up was < 6 months (30,31). Therefore firm conclusions on the effects of discontinuation rhGH supplementation cannot be made.

## **DISCUSSION**

In this study we demonstrated that adult GHD patients who discontinued rhGH replacement for various reasons do not show important adverse metabolic changes in the long-term. Fat mass increased without negatively affecting lipid profile, glucose metabolism, or bone mass. In addition, in older patients no changes were observed at all. It thus appears that rhGH replacement can be discontinued without negative metabolic effects in the long term, provided that routine cardiovascular clinical guidelines for the treatment of lipid abnormalities and hypertension are properly followed. We found a decrease in LDL- and total cholesterol in the presence of an increase in the use of lipid lowering medication after discontinuation. In the subgroup of patients aged > 60 years no significant metabolic changes after cessation of therapy were observed at all. Furthermore, we observed no changes in lumbar spine BMD or fasting glucose level. BMI even slightly decreased within the 3 year follow up period as did bone turnover markers, although the latter changes were not significant possibly due to the sample size. The only parameter that significantly deteriorated after discontinuation was fatpercentage as measured by DXA.

It is questionable whether the observed statistically significant changes are clinically relevant. At all time points, lipid- and fasting glucose concentrations remained within the

normal range in both groups and BMI even decreased after discontinuation of rhGH. In the general population, for every 1 mmol/L LDL-C reduction, the risk of major vascular events decreases by 20%(33). Given the adverse lipid profile in adult GHD patients that is associated with increased cardiovascular risk, it might be beneficial to start lipid-lowering medication in all middle-aged GHD patients. The clinical implications of the average 0.4 mmol/L increase in fasting glucose levels after discontinuation are less clear since fasting glucose levels remained within the normal range at all time points. It has been shown that the hazard ratio for coronary heart disease does not differ between patients with fasting glucose concentrations ranging between 3.9 and 5.6 mmol/L and the incidence of coronary heart disease increases with increasing BMI (34, 35). On average, all subjects would be classified as overweight at all time points, however since BMI might not be the best anthropometric predictor for cardiovascular events, the observed increase in fatpercentage might counteract the decrease in BMI after discontinuation (36). 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 rhGH replacement is associated with improvement of cardiovascular risk factors like lipid profile, bone mass, and quality of life (5,7,9,25, 32). However, data also show that the metabolic phenotype of GHD patients remains abnormal compared to the general population despite long-term replacement. Therefore, it is very well possible that the classic GHD phenotype might not be completely attributable to growth deficiency and/or that not all effects are reversible (11,12).

Since this is an observational study it obvious has limitations. 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 evaluate the effects on quality of life, another important indication for rhGH replacement. However, since this was an observational study, patients who might have benefitted most from rhGH replacement were less likely to have discontinued therapy for a prolonged period, and patients were also always asked for their physical and psychological well being during the visits. In case of severe deterioration of quality of life after discontinuation rhGH would have been re-initiated, as was reflected by the 10 patients that were identified prior to inclusion that re-initiated treatment within the first year.

In order to put our observations in the best perspective, we additionally performed a systematic literature search on studies reporting on discontinuation of rhGH 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 to 18 months. Overall, most studies reported that a parameter did not change without mentioning the outcome. This makes it hard to interpret these literature results since this implies that there was no change at all whereas the study only can report that there is no evidence of a difference (37). The majority of included patients had been on rhGH replacement for only 6-12 months prior to discontinuation whereas

some studies did not report the duration of therapy. This makes it difficult to interpret the results since the effects of rhGH are time dependent. For instance, a decrease in BMD might be observed within the first year affecting the effects of withdrawal when this occurs within the first year (7,9,18). Nevertheless, all studies reporting on body composition, including ours, have consistently shown an increase in fat percentage after discontinuation (27,20,30). Data on lipid profile after discontinuation were not conclusive, 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 of BMD after 18 months of discontinuation, although data on bone modifying agents including calcium and vitamin D were not available in this study (29). One study reported on patients (n=29) who used rhGH during a longer period of time (30). In the follow up period of 4 months in this study BMC and fatmass increased, lipid profile and quality of life scores however worsened and glucose level remained grossly unchanged. From all studies selected this study resembled our patient population at most and the reported results are comparable with ours although handling of statins and bisphosphonates were not mentioned.

The rationale for being restrictive with GH replacement in elderly patients is based upon the following. The GH/IGF-1 axis declines physiologically with ageing and smaller individuals within a species usually live longer (38). Additionally, the GH/IGF-1 axis has been linked with cancer risk and improved longevity (14), and functional mutations of the IGF-1R gene resulting in altered IGF-1 signalling appear to be more common in centenarians than in younger controls. Life span is also extended in mice lacking GHR, resulting in lower IGF-1 levels. Although these mutant mice lack other hormones, restoration of GH levels reverted their longevity to that of non-mutants (39, 40). Collectively, these results suggest that optimizing the GH/IGF-1 axis to promote healthy ageing in humans is more complex than originally appreciated, requires a greater understanding of its array of interactions 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. Since long-term replacement with rhGH generally will not normalize the metabolic profile and the beneficial effects of unrestricted GH replacement therapy especially in elderly GHD are yet inconclusive, we advise to reconsider the need to continue rhGH treatment of long-term treated GHD patients, and also explore alternative treatment strategies in patients, like a more stringent treatment of dyslipidaemia and hypertension, especially in those aged > 60 years. We advocate the initiation of further studies evaluating the effects of discontinuing GH replacement in the long-term enabling to determinate the optimal time point for withdrawal of growth hormone replacement.

**REFERENCES**

1. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism *Lancet* 1990;336:285-288.
2. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewar PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001;357:425-431.
3. Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen PH, Tanaka T & Thorner M. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. *Journal of Clinical Endocrinology and Metabolism* 1998; 83 (2): 382-95
4. Rosén T, Wilhelmsen L, Landin-Wilhelmsen K, Lappas G & Bengtsson BA. Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. *European Journal of Endocrinology* 1997; 137: 240-5
5. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. *J Clin Endocrinol Metab* 2004;89:2192-2199.
6. Cenci MC, Conceicao FL, Soares DV, Spina LD, Brasil RR, Lobo PM, Michmacher E, Vaisman M. Impact of 5 years of growth hormone replacement therapy on cardiovascular risk factors in growth hormone-deficient adults. *Metabolism* 2008;57:121-129.
7. Elbornsson M, Gotherstrom G, Bosaeus I, Bengtsson BA, Johannsson G, Svensson J. Fifteen years of GH replacement increases bone mineral density in hypopituitary patients with adult-onset GH deficiency. *Eur J Endocrinol* 2012;166:787-795.
8. Claessen KM, Appelman-Dijkstra NM, Adoptie DM, Roelfsema F, Smit JW, Biermasz NR, Pereira AM. Metabolic profile in growth hormone-deficient (GHD) adults after long-term recombinant human growth hormone (rhGH) therapy. *J Clin Endocrinol Metab* 2013;98:352-361.
9. Gotherstrom G, Svensson J, Koranyi J et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001; 86(10):4657-4665.
10. Koltowska-Haggstrom M, Mattsson AF, Monson JP et al. Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalise quality of life? *Eur J Endocrinol* 2006; 155(1):109-119.
11. Claessen KMJA, Appelman-Dijkstra NM, Pereira AM, Joustra SD, de Mutsert R, Gast KB, den Heijer M, Smit JWA, Dekkers OM & Biermasz NR. Abnormal metabolic phenotype in middle-aged GH-deficient adults despite long-term recombinant human GH replacement. *European Journal of Endocrinology* 2014; 170: 263-72
12. van der Klaauw AA, Romijn JA, Biermasz NR et al. Sustained effects of recombinant GH replacement after 7 years of treatment in adults with GH deficiency. *Eur J Endocrinol* 2006; 155(5):701-708.
13. Corpas E, Harman SM & Blackman MR. Human growth hormone and human aging. *Endocrine Reviews* 1993; 14 (1): 20-399. *European Journal of Endocrinology* 2011; 164 (5): 657-65
14. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J et al. A major reduction in pro-aging signalling, cancer and diabetes in humans. *Science Translational Medicine* 2011; 3 (70): 1-9
15. Kokshoorn NE, Biermasz NR, Roelfsema F, Smit JWA, Pereira AM & Romijn JA. GH replacement therapy in elderly GH-deficient patients: a systematic review. *European Journal of Endocrinology* 2011; 164 (5): 657-65
16. Janssen YJ, Frolich M, Roelfsema F. A low starting dose of genotropin in growth hormone-deficient adults. *J Clin Endocrinol Metab* 1997; 82(1):129-135.

17. Janssen YJH, Hamdy NA, Frolich M, Roelfsema F. Skeletal effects of two-years of treatment with low physiological doses of recombinant human growth hormone (GH) in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab* 1998; 83(6):2143-2148
18. Biermasz NR, Hamdy NA, Pereira AM, Romijn JA, Roelfsema F. Long-term skeletal effects of recombinant human growth hormone (rhGH) alone and rhGH combined with alendronate in GH-deficient adult: a seven-year follow-up study. *Clin Endocrinol* 2004; 60: 568-575.
19. Ghigo E, Aimaretti G, Corneli G. Diagnosis of adult GH deficiency. *Growth Horm IGF Res* 2008, Feb;18(1):1-16.
20. Aimaretti G, Corneli G, Rovere S, Granata R, Baldelli R, Grottoli S, Ghigo E, Insulin-Like Growth Factor I Levels and the Diagnosis of Adult Growth Hormone Deficiency. *Horm Res Paediatr* 2004;62(suppl 1):26-33
21. Grinspoon SK, Biller BM. Clinical review 62: laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab.* 1994;79:923–931.
22. Fish HR, Chernow B, O'Brian JT. Review Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: a review. *Metabolism.* 1986 Aug; 35(8):763-80.
23. Courtney CH, McAllister AS, McCance, Hadden, Leslie H, Sheridan B, Atkinson AB. The insulin hypoglycaemia and overnight metyrapone tests in the assessment of the hypothalamic-pituitary-adrenal axis following pituitary surgery. *Clin Endocrinol (Oxf)* 2000;53:309–312.
24. Maghnie M, Uga E, Temporini F, Di IN, Secco A, Tinelli C, Papalia A, Casini MR, Loche S. Evaluation of adrenal function in patients with growth hormone deficiency and hypothalamic-pituitary disorders: comparison between insulin-induced hypoglycemia, low-dose ACTH standard ACTH and CRH stimulation tests. *Eur J Endocrinol.* 2005;152:735–741.
25. Appelman-Dijkstra NM, Claessen KMJA, Hamdy NAT, Pereira AM, Biermasz NR. Effects of up to 15 years of recombinant human GH (rhGH) replacement on bone metabolism in adults with Growth Hormone Deficiency (GHD): The Leiden Cohort Study. *Clin Endo Epub* 2014 Nov;81(5):727-35.
26. Fukuda I, Hizuka N, Yasumoto K, Morita J, Kurimoto M & Takano K. Metabolic co-morbidities revealed in patients with childhood-onset adult GH deficiency after cessation of GH replacement therapy for short stature. *Endocrine Journal* 2008; 55: 977-84
27. Yuen KCJ, Dunger DB, Persisting effects on fasting glucose levels and insulinsensitivity after 6 months of discontinuation of a very low-dose GH therapy in adults with severe GH deficiency *Clinical Endocrinology* (2006) 64, 549–555
28. Colao A, di Somma C, Rota F, Pivonello R, Savanelli MC, Spiezia S & Lombardi G. Short-term effects of growth hormone (GH) treatment or deprivation on cardiovascular risk parameters and intima-media thickness at carotid arteries in patients with severe GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2005; 90 (4): 2056-62
29. Biller BMK, Sessimo G, Baum HBA, Hayden D, Schoenfeld D & Klibanski A. Withdrawal of long-term physiological growth hormone (GH) administration: differential effects on bone density and body composition in men with adult-onset GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2000; 85 (3): 970-6
30. Filipsson Nyström H, Barbosa EJJ, Nilsson AG, Norrman L, Ragnarsson O & Johannsson G. Discontinuing long-term GH replacement therapy – A randomized, placebo-controlled crossover trial in adult GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2012; 97 (9): 3185-95
31. McMillan CV, Bradley C, Gibney J, Healy ML, Russell-Jones DL, Sönksen PH, Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency *Clinical Endocrinology* (2003)59, 467–475
32. Mo D, Blum MD, Rosilio M, Webb SM, Qi R, Strassburger CJ, Ten-Year Change in Quality of Life in Adults on Growth Hormone (GH) Replacement for GH Deficiency: An Analysis of the Hypopituitary

- Control and Complications Study (HypoCCS). *Journal Clinical Endocrinology and Metabolism*. 2014 Sep 18. [Epub ahead of print]
33. Cholesterol Treatment Trialists' (CTT) Collaborators: Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R & Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; 366 (9493): 1267-78
  34. Emerging Risk Factors Collaboration: Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK & Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375 (9733): 2215-22
  35. Brixner DI, Bron M, Bellows BK, Ye X, Yu J, Raparla S & Oderda GM. Evaluation of cardiovascular risk factors, events, and costs across four BMI categories. *Obesity* 2013; 21 (6): 1284-92
  36. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F & Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006; 368 (9536): 666-78
  37. Altman DG, Bland JM. Absence of evidence is not evidence of absence *BMJ*. 1995 Aug 19;311(7003):485
  38. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. *Diabetes* 2012; 61(6):1315-1322.
  39. Russell SJ, Kahn CR. Endocrine regulation of ageing. *Nat Rev Mol Cell Biol* 2007; 8(9):681-691.
  40. Tatar M, Bartke A, Antebi A. The endocrine regulation of aging by insulin-like signals. *Science* 2003; 299(5611):1346-1351.
  41. Holmes SJ, Whitehouse RW, Economou G, O'Halloran DJ, Adams JE, Shalet SM. Further increase in forearm cortical bone mineral content after discontinuation of growth hormone replacement. *Clin Endocrinol (Oxf)*. 1995 Jan;42(1):3-7.
  42. Gómez JM, Gómez N, Fiter J, Soler J. Effects of long-term treatment with GH in the bone mineral density of adults with hypopituitarism and GH deficiency and after discontinuation of GH replacement. *Horm Metab Res*. 2000 Feb;32(2):66-70.