Change in baseline characteristics over 20 years of adults with growth hormone (GH) deficiency on GH replacement therapy

Charlotte Höybye¹, Pia Burman², Ulla Feldt-Rasmussen³, Judith Hey-Hadavi⁴, Ferah Aydin⁵, Cecilia Camacho-Hubner⁴ and Anders F Mattsson⁵

¹Patient Area Endocrinology and Nephrology, Inflammation and Infection Theme, Karolinska University Hospital and Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden, ²Department of Endocrinology, Skåne University Hospital, University of Lund, Lund, Sweden, ³Department of Medical Endocrinology and Metabolism, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, ⁴Endocrine Care, Pfizer Inc., New York, New York, USA, and ⁵Endocrine Care, Pfizer Health AB, Sollentuna, Sweden

Correspondence should be addressed to C Höybye
Email
charlotte.hoybye@sl.se

Abstract

Objective: Clinical observations over time of adults with growth hormone (GH) deficiency (GHD) have indicated a shift in patient characteristics at diagnosis. The objective of this study was to compare baseline characteristics of patients diagnosed with adult-onset GHD naive to GH replacement during three study periods (1994–1999 (P1), 2000–2004 (P2), and 2005–2012 (P3)) using the KIMS (Pfizer's International Metabolic) database.

Methods: Data were retrieved for a total of 6069 patients with adult-onset GHD from six countries (Belgium, Germany, Netherlands, Spain, Sweden, and UK): P1 ($n = 1705$), P2 ($n = 2397$), and P3 ($n = 1967$).

Results: The proportions of patients with pituitary/hypothalamic tumors and patients with multiple pituitary hormone deficiencies decreased per entry year period, while the proportions with hypertension and diabetes increased. The lag time from diagnosis of pituitary disease to start of GH treatment decreased by 2.9 years over the entry year periods. IGF-1 increased by 0.1 standard deviation score per entry year period. Maximum GH following various stimulation tests, BMI, and waist circumference increased. The use of radiotherapy, glucocorticoid replacement doses, and the proportion of women >50 years on estrogen replacement therapy decreased. The effects of 1 year of GH replacement were similar over the entry year periods despite changes in the patients' baseline characteristics. An expected increase in fasting blood glucose was seen after 1 year of GH treatment.

Conclusions: The degree of confirmed GHD became less pronounced and more patients with co-morbidities and diabetes were considered for GH replacement therapy, possibly reflecting increased knowledge and confidence in GH therapy gained with time.

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Introduction

Treatment with growth hormone (GH) started in the late 1950s when enough cadaveric GH was purified to treat patients with GH deficiency (GHD). During the early decades of treatment, only children received GH and the goal was primarily to promote longitudinal growth. The number of patients diagnosed with GHD was relatively low,

supplies were scarce, and treatment expensive. Monitoring of efficacy was clinical and limited to measurement of height and body proportions. Moreover, conclusions on potential side effects, such as diabetes, cardiovascular diseases, and cancer, were from the clinical picture of GH excess (acromegaly). Of note, the initial studies used

body weight-adjusted GH doses and some adults obtained supraphysiological GH levels with elevated insulin-like growth factor 1 (IGF-1) concentrations (1). The treatment effects of GH replacement therapy may therefore have been overestimated in initial pivotal studies. In the late 1980s, when recombinant human GH (rhGH) became available, interest in the profound metabolic effects of GH intensified and the beneficial effects of rhGH treatment in adults with GHD were demonstrated (2, 3, 4). Since then, many studies have been published, most of them reporting on a few years of GH treatment but some on longer treatment duration (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). Typical manifestations of GHD in adulthood are well-defined and include an abnormal body composition, fatigue, decreased physical activity, an adverse cardiovascular risk profile, and reduced quality of life (QoL) (5, 6). In addition, adults with pituitary insufficiency have demonstrated a shorter lifespan compared to healthy controls (7, 8, 9, 10, 11, 12, 13, 14, 15, 16). Previously, the excess mortality was considered to be caused by cardiovascular disease (7, 8) but, in recent decades, other causes such as adrenal crises during infections and secondary brain tumors following radiotherapy have been revealed to explain most premature deaths (16). Since 1990, GH replacement therapy has been prescribed to adults with GHD according to specific diagnostic criteria and several clinical trials have documented that GH improves body composition, cardiovascular risk factors and QoL (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20).

In the clinical setting, it appears that the phenotype of patients treated for GHD as adults has shifted over time. The primary aim of this study was to explore this clinical observation by systematically comparing baseline characteristics of patients with adult-onset GHD naïve to GH replacement in whom GH treatment was initiated between 1994 and 2012. The secondary aim was to describe the effects of GH replacement after 1 year during this period.

Patients and methods

Data were retrieved from 1994 to 2012 using KIMS (Pfizer's International Metabolic Database). KIMS was launched in 1994 and closed for the input of further data in 2012. The database contains prospectively collected observational data from almost 16 000 adult patients with GHD from 31 countries. Data for the current study were retrieved from six countries (Belgium, Germany, Netherlands, Spain, Sweden, and UK), which enrolled the highest numbers

of patients with adult-onset GHD naïve to GH treatment and had patients well represented over time. Data were derived from a total of 6069 patients over three defined time periods: 1994–1999 (P1) ($n=1705$), 2000–2004 (P2) ($n=2397$), and 2005–2012 (P3) ($n=1967$).

Information regarding medical history, gender, age at diagnosis, age at GHD diagnosis and at start of GH treatment, GH dose, anthropometry, cardiovascular risk factors, and QoL was collected. The diagnosis of GHD was at the treating physician's discretion based on GH stimulation tests, clinical manifestations, and medical history. For the purpose of this study, severe GHD was defined as peak GH <3 $\mu\text{g/L}$ after insulin-induced hypoglycemia or a glucagon-stimulation test, peak GH <0.4 $\mu\text{g/L}$ after arginine-stimulation test, body mass index (BMI)-adjusted cut-offs after growth hormone-releasing hormone (GHRH)-arginine test, IGF-1 standard deviation score (SDS) <-2 , and three or more additional pituitary deficiencies.

The following variables were assessed at baseline and after 1 year of GH treatment: IGF-1, BMI, waist circumference, body fat, lean body mass, blood pressure, blood lipids, glucose, hemoglobin A1c (HbA1c), and QoL. Serum IGF-1 concentrations were measured at a central facility by radioimmunoassay after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) from 1994 to 2002 and by chemiluminescence immunoassays from 2003 to 2004 (Nichols Advantage® System) and from 2005 to 2012 (Immulin 2500, DPC Siemens). For each assay, age- and gender-specific reference ranges were used to determine IGF-1 SDS. Reference ranges and consistency of IGF-1 SDS values between assays were validated internally. Body composition was evaluated by dual-energy X-ray absorptiometry (DXA) and bioelectric impedance analysis. Total body fat and lean body mass were determined from the DXA measurements, and body fat and fat-free mass were calculated from the bio-impedance measurements.

Hypertension was defined as blood pressure $>130/80$ mmHg, treatment with antihypertensive medication, or hypertension reported in medical history. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured centrally. Serum low-density lipoprotein (LDL) cholesterol concentrations were calculated using Friedewald's formula (21). A total cholesterol concentration >5.20 mmol/L (>201 mg/dL) or treatment with cholesterol-lowering medication was considered as evidence of abnormal levels. Fasting blood glucose and HbA1c were analyzed locally. HbA1c levels $\geq 6.5\%$ or treatment with

antidiabetic medication was consistent with a diagnosis of diabetes (22). QoL was assessed using the QoL assessment of GHD in adults (QoL-AGHDA) questionnaire (23, 24). Higher numerical scores, to a maximum of 25, denote poorer QoL.

GH dosing was at the discretion of treating physicians and reported to the KIMS database. GH dose was analyzed as the starting dose (i.e., dose prescribed at the entry visit into KIMS) and the dose reported at the visit after 1 year of treatment. Concomitant medication for treatment of diabetes, hypercholesterolemia, hypertension, and pituitary deficiency replacement was summarized as yes or no. Glucocorticoid doses were expressed as hydrocortisone equivalent dose (mg/day) (25) and thyroxine dose as µg/day.

Means, standard deviations (SDs), and proportions (percentages) were calculated depending on the type of variable. Trend tests for dichotomous variables were performed with the χ^2 test and Cochran-Armitage test over entry year periods. Linear regression models were applied with adjustment for age and gender. Adjustment was additionally performed by baseline value for analyses of numerical delta variables. 'P trend' in the text stands for in analyses of means the *P* value under 'no change' in the linear yearly trend, and in analyses of proportions under 'no change' in the trend over the time periods. Overall

mean or proportion stands for the mean or proportion taken over all entry years. Statistical significance was set at $P < 0.05$. The level for confidence intervals (CIs) was 95%. Analyses were performed with SAS 9.4 procedures PROC FREQ, PROC GLM, PROC GENMOD, and PROC SGPLOT (SAS Institute Inc., Cary, NC, USA).

Results

The total cohort consisted of 2995 (49%) male and 3074 (51%) female patients and the gender ratio was stable over the entry year periods (Table 1). The proportion of patients with pituitary surgery alone increased from 52 to 63% over the entry year periods (P -trend < 0.001) (Table 1), while the use of radiotherapy markedly decreased (Fig. 1 and Table 1). The most frequent pituitary tumors over all entry year periods were non-functioning pituitary adenoma ($n = 2046$) followed by prolactinoma ($n = 607$) and corticotropinoma ($n = 472$). However, many patients ($n = 2376$) had other etiologies causing GHD. Among these, the most frequent were postpartum necrosis ($n = 225$), empty sella ($n = 178$), and traumatic brain injury ($n = 154$). The proportion of patients with tumors in the pituitary and hypothalamic area decreased over time from 79 to 67% (P -trend < 0.0001) (Fig. 1 and Table 1). Likewise, the

Table 1 Baseline characteristics given as percentage of patients with adult-onset GHD deficiency enrolled in KIMS database according to entry year period ($n = 6069$).

Characteristic	Percentage			P value trend
	P1 (1994–1999) ($n = 1705$)	P2 (2000–2004) ($n = 2397$)	P3 (2005–2012) ($n = 1967$)	
Gender (women)	49	51	51	0.33
Pituitary/hypothalamic tumors	79	74	67	< 0.0001
Surgery alone in PHT patients	52	56	63	< 0.0001
Radiotherapy in PHT patients	47	39	29	< 0.0001
Peak GH > 3 µg/L after ITT	3.0	5.8	11.4	< 0.0001
Confirmed severe GHD	70	65	63	< 0.0001
Multiple hormone deficiencies	93	91	87	< 0.0001
Thyroxine treatment in TSH-deficient patients	92	86	86	< 0.0001
Estrogen treatment in women > 50 years	41	26	11	< 0.0001
Estrogen treatment in women > 50 years with FSH/LH deficiency	48	36	17	< 0.0001
Diabetes mellitus	8.1	9.8	12.0	< 0.0001
Antidiabetic medication in diabetic patients	36	45	53	0.0002
Total cholesterol > 5.2 mmol/L or lipid-lowering medication (abnormal)	77	71	67	< 0.0001
Lipid-lowering medication in all patients	7.2	10.9	12.0	< 0.0001
Lipid-lowering medication in patients with abnormal values	14	28	35	< 0.0001
Coronary heart disease	5.9	4.9	3.2	0.0001
Stroke	3.8	1.7	1.5	< 0.0001

ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHD, growth hormone deficiency; LH, luteinizing hormone; ITT, insulin tolerance test; PHT, pituitary/hypothalamic tumor; TSH, thyroid-stimulating hormone.

Figure 1

Six selected dichotomous baseline characteristics by entry year. DF, luteinizing hormone/follicle-stimulating hormone deficient; GHD, growth hormone deficiency; PH, pituitary hypothalamic; RT, radiotherapy. Abnormal lipids = total cholesterol >5.2 mmol/L or on lipid-lowering medication.

proportion of patients with multiple pituitary hormonal deficiencies decreased from 93 to 87% (P -trend <0.0001) and further analyses showed reduced rates of all other pituitary deficiencies (Table 1).

Mean age at diagnosis of the pituitary disease and mean age at diagnosis of GHD gradually increased from 40.4 years in P1 to 43.9 years in P3 (3.84 months per entry year; P -trend <0.0001) and from 46.2 years in P1 to 48.0 years in P3 (P -trend 0.001), respectively (Table 2). In contrast, the lag time from diagnosis of pituitary disease and start in KIMS decreased by 2.9 years over the entry year periods (i.e., 3.3 months per entry year; P -trend <0.0001) (Table 2). For the entire cohort, the lag time from diagnosis of pituitary disease to GHD diagnosis decreased 1.8 years over the entry year periods (i.e., 2.2 months per entry year; P -trend <0.0001). The time from diagnosis of GHD to start in KIMS decreased by 1.1 years over the entry year periods (i.e., 1.1 months per entry year; P -trend <0.0001). Overall, GHD was diagnosed

with one or more stimulation tests in approximately 93% of the patients: insulin-stimulation test in 55%, arginine-stimulation test in 13%, and glucagon-stimulation test in 10%, while other tests (e.g., clonidine-stimulation test, 24-h GH profile, insulin/arginine-stimulation test) were used in the remaining patients. The use of an arginine-stimulation test decreased over the entry year periods, whereas there were no changes in the other diagnostic test methods and number of tests used over time (data not shown). The mean maximum GH level after insulin-stimulation test increased from 0.75 μ g/L in P1 to 1.26 μ g/L in P3 (P -trend <0.0001) (Table 2). The mean maximum GH level also increased after the arginine-stimulation test, but there was no change after the glucagon-stimulation test. Of note, the proportion of patients with maximum GH >3 μ g/L after insulin-stimulation testing increased from 3.0% in P1 to 11.4% in P3 (P -trend <0.0001; Table 1) and the proportions of patients with confirmed severe GHD decreased from 70% in P1 to 63% in P3 (P -trend <0.0001).

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Table 2 Analysis of selected background characteristics in patients with adult-onset GHD deficiency by time period and change estimate by individual entry year ($n = 6069$).

Characteristic	Entry year period, mean (s.d.)			Linear trends (1995–2012)	
	P1 (1994–1999) ($n = 1705$)	P2 (2000–2004) ($n = 2397$)	P3 (2005–2012) ($n = 1967$)	Change/entry year (95% CI)	P value trend
Age at diagnosis of pituitary disease (years)*	40.4 (14.1)	42.2 (14.2)	43.9 (13.8)	0.32 (0.23–0.40)	<0.0001
Age at GHD diagnosis (years)*	46.2 (13.5)	47.4 (13.4)	48.0 (13.0)	0.14 (0.055–0.22)	0.001
Time from pituitary disease to KIMS start (years) [†]	8.3 (8.2)	7.0 (8.0)	5.4 (7.2)	–0.28 (–0.33 to –0.23)	<0.0001
Time from pituitary disease diagnosis to GHD diagnosis (years) [†]	6.0 (8.0)	5.4 (7.6)	4.2 (6.8)	–0.18 (–0.22 to –0.13)	<0.0001
Time from GHD diagnosis to KIMS start (years) [†]	2.3 (3.9)	1.7 (3.4)	1.2 (2.9)	–0.09 (–0.12 to –0.07)	<0.0001
Age at KIMS start (years)*	48.5 (12.9)	49.1 (13.0)	49.2 (12.9)	0.04 (–0.04 to 0.12)	0.34
Maximum GH peak ($\mu\text{g/L}$) [‡]					
After insulin-stimulation test ^{##}	0.75 (0.99)	0.88 (1.18)	1.26 (1.87)	0.04 (0.028–0.053)	<0.0001
After arginine-stimulation test ^{##}	0.81 (1.89)	0.97 (1.50)	1.41 (2.47)	0.05 (0.014–0.080)	0.005
After glucagon-stimulation test ^{###}	0.67 (0.68)	0.67 (0.95)	0.74 (0.90)	0.014 (–0.008 to 0.033)	0.22
Thyroxine dose ($\mu\text{g/day}$) [†]	114 (40)	107 (40)	95 (36)	–1.8 (–2.1 to 1.5)	<0.0001
Hydrocortisone equivalent dose (mg/day) [†]	24.1 (9.9)	22.1 (9.7)	19.3 (10.0)	–0.45 (–0.53 to –0.37)	<0.0001

*Adjusted for gender (50%). [†]Adjusted for age at KIMS start and gender. [‡]Patients with values >20 $\mu\text{g/L}$ were excluded. ^{##}P1 ($n = 863$), P2 ($n = 1244$), and P3 ($n = 960$). ^{###}P1 ($n = 295$), P2 ($n = 290$), and P3 ($n = 162$). ^{####}P1 ($n = 116$), P2 ($n = 284$), and P3 ($n = 173$).

GH, growth hormone; GHD, growth hormone deficiency; SD, standard deviation.

(Fig. 1 and Table 1). At baseline, the proportion of patients with thyroxine treatment decreased from 92% in P1 to 86% in P3 (P -trend <0.0001) (Table 1). Baseline thyroxine dose decreased from 114 $\mu\text{g/day}$ in P1 to 95 $\mu\text{g/day}$ in P3 (P -trend <0.0001) (Table 2). The mean thyroxine dose decreased on average by 1.8 $\mu\text{g/day}$ per entry year (P -trend <0.0001). The mean baseline glucocorticoid replacement dose (in hydrocortisone equivalents) decreased over the periods from 24.1 mg/day in P1 to 19.3 mg/day PD, i.e., a mean decrease of 0.45 mg/day per entry year (P -trend <0.0001) (Table 2). Estrogen treatment decreased markedly in women >50 years of age from 41% in P1 to 11% in P3 (P -trend <0.0001) (Fig. 1 and Table 1).

Mean waist circumference increased from 97.4 cm in P1 to 100.1 cm in P3 (P -trend <0.0001) and mean BMI increased from 28.8 kg/m² in P1 to 29.6 kg/m² in P3 (0.07 per entry year; P -trend <0.0001) (Table 3). In line with observations for BMI and waist circumference, body fat values increased by entry year (0.16 kg per year; P -trend <0.0037) as measured by bioelectric impedance analysis. Measurements of body fat with DXA showed similar results despite smaller number of observations (Table 3).

Mean baseline IGF-1 SDS increased over the observation period (P1 = –1.97, P2 = –1.37, and P3 = –0.94). The linear increase in baseline values was 0.1 SDS per entry year (P -trend <0.0001) (Table 3). The proportion of patients with abnormal cholesterol decreased from 77% in P1 to 67% in P3 (P -trend <0.0001). Mean total cholesterol decreased from 6.08 mmol/L in P1 to 5.46 mmol/L in

P3 (P -trend <0.0001) (Table 3). HDL cholesterol did not change in a clinically meaningful manner over the entry year periods (P -trend 0.03), while mean LDL cholesterol decreased from 3.8 mmol/L in P1 to 3.2 mmol/L in P3 (P -trend <0.0001) along with an increased percentage of patients treated with lipid-lowering medication from 7.2% in P1 to 12.0% in P3 (P -trend <0.0001) (Fig. 1 and Table 1). Fasting blood glucose increased from 4.95 mmol/L in P1 to 5.23 mmol/L in P3, i.e., a 0.03 mmol/L change per entry year (P -trend <0.0001) and HbA1c increased from 5.16% in P1 to 5.52% in P3, i.e. a 0.04% change per entry year (P -trend <0.0001) (Table 3). The number of patients with diabetes mellitus increased over the observation period (P1=8.1%, P2=9.8, and P3=12.0%; P -trend <0.0001) as did those receiving antidiabetic treatment (P1=36%, P2=45%, and P3=53%; P -trend 0.0002) (Table 1).

Blood pressure was clinically unchanged over the entry year periods (Table 3). The number of patients diagnosed with hypertension increased (P1=34%, P2=38%, and P3=39%; P -trend 0.0026), as did the numbers on antihypertensive drugs (P1=32%, P2=43%, and P3=39%; P -trend 0.03) (Table 1). The number of patients smoking decreased (P1=20%, P2=17%, and P3=13%; P -trend <0.0001). The proportion of patients with a history of cancer was similar over the entry year periods (data not shown). The prevalence of patients with coronary heart disease or stroke decreased over the entry year periods (Table 1). Baseline QoL-AGHDA score worsened from 10.8 in P1 to 13.1 in P3 (P -trend

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Table 3 Mean analyses of baseline (BL) and first treatment-year changes in selected endpoints in 6069 adults with growth hormone (GH) deficiency (GHD).

Endpoint	Analysis	Entry year period*, mean (S.E.M.)			Linear trend analysis over entry years (1995–2012)	
		P1 (1994–1999) (n = 1705)	P2 (2000–2004) (n = 2397)	P3 (2005–2012) (n = 1967)	P value change per entry year	BL [†] or Δ [‡] values (95% CI)
IGF-1 SDS	BL	−1.97 (0.04)	−1.37 (0.04)	−0.94 (0.05)	<0.0001	0.11 (0.09–0.12)
BL: −1.48	Δ	2.14 (0.04)	1.87 (0.04)	1.73 (0.05)	<0.0001	1.93 (1.89–1.98)
GH dose	BL	0.18 (0.005)	0.20 (0.004)	0.19 (0.005)	0.11	0.0008 (0.0002–0.002)
BL: 0.19 mg/day	Δ	0.18 (0.005)	0.13 (0.004)	0.11 (0.005)	<0.0001	0.14 (0.13–0.15)
BMI	BL	28.8 (0.14)	29.2 (0.12)	29.6 (0.13)	0.0001	0.07 (0.03–0.11)
BL: 29.2 kg/m ²	Δ	−0.02 (0.05)	−0.06 (0.04)	0.12 (0.05)	0.005	0.002 (−0.05 to 0.05)
Waist	BL	97.4 (0.36)	98.5 (0.32)	100.1 (0.35)	<0.0001	0.25 (0.16–0.34)
BL: 98.4 cm	Δ	−1.9 (0.19)	−1.4 (0.17)	−0.2 (0.20)	<0.0001	−1.20 (−1.40 to −0.98)
BL: 129 mmHg	Δ	0.10 (0.42)	−0.4 (0.37)	−0.2 (0.45)	0.96	0.01 (−0.45 to 0.48)
Cholesterol	BL	6.08 (0.04)	5.71 (0.04)	5.46 (0.04)	<0.0001	−0.05 (−0.06 to −0.04)
BL: 5.76 mmol/L	Δ	−0.29 (0.03)	−0.33 (0.03)	−0.29 (0.04)	0.84	−0.30 (−0.34 to −0.26)
LDL-cholesterol	BL	3.83 (0.03)	3.50 (0.03)	3.23 (0.04)	<0.0001	−0.056 (−0.064 to −0.047)
BL: 3.54 mmol/L	Δ	−0.26 (0.03)	−0.31 (0.03)	−0.21 (0.03)	0.21	−0.27 (−0.30 to −0.23)
Fasting blood glucose	BL	4.95 (0.04)	5.08 (0.04)	5.23 (0.05)	<0.0001	0.03 (0.02–0.04)
BL: 5.06 mmol/L	Δ	0.22 (0.04)	0.26 (0.04)	0.23 (0.05)	0.98	0.24 (0.18–0.29)
HbA1c	BL	5.16 (0.03)	5.49 (0.02)	5.52 (0.03)	<0.0001	0.036 (0.029–0.046)
BL: 5.38%	Δ	0.04 (0.02)	0.17 (0.02)	0.11 (0.02)	0.01	0.11 (0.08–0.13)
QoL-AGHDA score	BL	10.8 (0.20)	12.9 (0.18)	13.1 (0.20)	<0.0001	0.22 (0.18–0.27)
BL: 12.4 yes-items	Δ	−4.5 (0.18)	−4.5 (0.17)	−3.8 (0.21)	0.001	−4.3 (−4.5 to −4.0)
Physical activity	BL	34.6 (0.72)	32.7 (0.65)	31.6 (0.77)	0.0005	−0.33 (−0.53 to −0.15)
BL: 32.8	Δ	9.0 (0.82)	10.7 (0.76)	8.1 (0.99)	0.26	9.5 (8.5–10.4)

Δ: First treatment-year delta analysis in which the entry year periods are compared assuming the same baseline value and analyses are also controlled for age and gender.

*Baseline analysis adjusted for age to 50 years and gender to 50% males; [†]BL: change/entry year (95% CI); [‡]Δ: overall mean (95% CI).

BL, baseline; CI, confidence interval; LDL, low-density lipoprotein; QoL-AGHDA, quality of life-assessment of growth hormone deficiency in adults; SDS, standard deviation score.

<0.0001) (Table 3), i.e. mean linear increase of 0.2 score items per entry year. GH dose at baseline was unchanged over the over the entry year periods (*P*-trend 0.11) (Table 3).

The mean GH dose during the first year of treatment decreased from 0.18 mg/day in P1 to 0.11 mg/day in P3 (*P*-trend <0.00019) (Table 3); thus, the highest doses were administered in P1. The overall mean change in IGF-1 SDS from baseline to 1 year after GH treatment was 1.93 SDS, with the largest change in P1 and lowest in P3 (*P*-trend <0.0001) (Fig. 2). BMI was unchanged, but mean waist circumference was 1.20 cm less after 1 year of GH treatment, with greater change in earlier periods (*P*-trend <0.0001) (Table 3). The overall mean decrease in body fat during the first year of GH treatment was 1.07 kg as assessed by bioelectric impedance analysis (95% CI −1.40 to −0.73; *P* < 0.05) (Table 3). The change was similar during three entry year periods (*P*-trend = 0.12). However, the cross-sectional body fat values both at baseline and at 1 year of GH treatment were higher during later entry

year periods (Table 3). Overall, there was a statistically significant increase of 1.05 kg in free lean mass during the first year of GH treatment as assessed by bioelectric impedance analysis (95% CI 0.79–1.32; *P* < 0.05) (Table 3). The change was similar during three entry year periods (*P*-trend = 0.88). The results for DXA measurements were comparable to bioelectric impedance analysis measurements (Table 3). Blood pressure remained stable over the first year of GH treatment across the entry year periods (Table 3). With respect to the overall change in lipids over the first year of the entry year periods (Table 3), mean total cholesterol decreased by 0.30 mmol/L, mean LDL cholesterol decreased in parallel with total cholesterol, no change was seen for HDL cholesterol, and mean triglycerides decreased by 0.12 mmol/L. During the first year of GH treatment, overall mean fasting glucose concentration increased by 0.24 mmol/L and HbA1c by 0.11%, with similar changes across the entry year periods (Fig. 2 and Table 3). Mean decrease in QoL-AGHDA scores after 1 year of GH replacement was higher in P1 and P2

Figure 2

Means for six selected numerical end-point variables by baseline and first year visit over entry years. Circumf, circumference; F, fasting; GH, growth hormone; IGF-1, insulin-like growth factor 1; QoL-AGHDA, quality of life assessment of growth hormone deficiency in adults. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-19-0576>.

compared to P3, with an overall mean decrease of 4.3 score-items across the entry year periods (Table 3).

Discussion

In this study, we examined baseline characteristics of 6069 patients with adult-onset GHD enrolled in KIMS from 1994 to 2012. We found that over time the degree of confirmed GHD became less pronounced and patients with diabetes mellitus were more frequently considered for GH replacement. Hydrocortisone and thyroxine doses decreased over time. The proportion of women >50 years of age receiving treatment with estrogen decreased. Baseline BMI, body fat, fasting blood glucose, and HbA1c increased; QoL became poorer; and the lipid profile became more favorable. The patients enrolled during the initial years were treated with the highest GH doses

after one year, but the changes in body composition and metabolic variables were similar over the entire study period.

Over the years, the etiology of GHD has changed, with fewer patients having pituitary adenomas. The proportion of patients who underwent pituitary surgery for pituitary adenomas increased, whereas fewer were treated with radiotherapy. Hypopituitarism is a well-known adverse effect of radiotherapy (5) and, with fewer patients receiving this treatment, GHD and other pituitary hormone deficiencies would be expected to decrease. Improvement of surgical techniques should have contributed to this effect. On the other hand, more patients with other underlying diseases causing hypopituitarism were enrolled. This might reflect an accumulation of experience and confidence in GH treatment as well as a consequence of a greater accessibility to GH, resulting in an increased possibility to treat patients.

The finding that patients with GHD were diagnosed and treated with GH at an earlier point in time likely contributed to a less profound GHD phenotype. Firstly, the maximal GH response to stimulation tests, although still consistent with guidelines (3, 5), increased over the years, as did IGF-1 SDS. Furthermore, the lag time from the diagnosis of GHD to initiation of GH treatment decreased. Based on these findings, less pronounced consequences of GHD would be anticipated. Surprisingly, QoL-AGHDA scores increased, indicating worsening of QoL across the entry year periods. This possibly reflects a patient selection bias, that is, the change in the underlying etiology of GHD: for example, the increase in the proportion of patients with traumatic brain injury may affect QoL. Alternatively, patients with poor QoL were more likely to receive GH treatment.

Hydrocortisone doses decreased over the entry year periods, which is in accordance with guidelines (26). Less expected was the decrease in thyroxine doses that was observed. This finding is seemingly in disagreement with a previous study which reported an under-treatment of central hypothyroidism based on measurements of serum free thyroxine (27). However, as the present study indicates milder pituitary insufficiency and, thereby, milder central hypothyroidism, the required thyroxine dose would be lower. The marked decrease in estrogen use amongst women >50 years of age is probably a consequence of more recent standard of care, mainly brought about by the Women's Health Initiative Study in which an association between estrogen replacement therapy after menopause and cardiovascular risk was reported (28).

The current study showed a decrease over the entry year periods in GH doses after 1 year of treatment. We interpret this as a consequence of the patients becoming less GH deficient over time as discussed previously.

In line with previous studies, we found that during the study period baseline values of BMI, fasting plasma glucose, and HbA1c as well as the proportion of patients treated with antidiabetic medication increased across the entry year periods (29). The prevalence of diabetes mellitus has increased substantially in the background population in all countries from 4.7% in 1980 to 8.5% in 2014 (30, 31). Therefore, it seems likely that of the present findings can be, in part, related to this global change in diabetes prevalence. The baseline lipid profile became more favorable, although this was confounded by the increase in the proportion of patients on cholesterol-lowering medications, which likely reflects improvements in preventive care with respect to cardiovascular disease.

Moreover, the decrease in severity of GHD, fewer women on estrogen treatment, and fewer patients with thyroid-stimulating hormone deficiency probably played a role, especially the latter which has been shown to have a stronger influence on lipids than GHD (27). KIMS is an international observational database of patients with metabolic diseases enrolled by the treating physicians who also provided information on the results of diagnostic tests and treatment. There might have been some variations in the enrolled patients between countries patients from countries with similar healthcare environments were evaluated in the present report. Particular strengths of the study were the large number of patients and the central analysis of IGF-1. In conclusion, the underlying etiology and baseline characteristics of patients with the adult-onset GHD has shifted over time. Patients have become more overweight but have a normal distribution between total body fat and lean body mass, possibly a combined result of lower doses of glucocorticoids, shorter lag time between the diagnosis of pituitary disease and start of GH replacement, and less pronounced GHD over time. Baseline glucose and HbA1c levels as well as the proportion of patients with diabetes mellitus has increased, while the lipid profile improved as a combined result of more intense use of lipid-lowering medication, less severe GHD, fewer patients with thyroid-stimulating hormone deficiency, lower glucocorticoid supplementation, and GH treatment. The expected effects of 1 year of GH replacement were noticed with an increase in IGF-1, lean body mass and fasting glucose while waist circumference, body fat, total and LDL cholesterol and QoL-AGHDA all increased. Our results suggest that the earlier commencement of GH replacement in adults in current clinical practice prevents development of a severe GHD phenotype and thus aims toward maintenance of several metabolic, physiologic and psychosocial variables rather than towards their normalization. This paradigm shift is of importance for the initiation and evaluation of GH-replacement in current GHD patients.

Declaration of interest

C Höybye is a KIMS investigator. P Burman and U Feldt-Rasmussen are members of the KIMS Steering Committee. J Hey-Hadavi, F Aydin, C Camacho-Hubner, and A F Mattsson are full time employees of Pfizer Inc.

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References

- Bengtsson BA, Edén S, Lönn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tölli J, Sjöström L & Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 309–317. (<https://doi.org/10.1210/jcem.76.2.8432773>)
- Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen T, Skakkebaek NE & Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1989 **1** 1221–1225. ([https://doi.org/10.1016/s0140-6736\(89\)92328-3](https://doi.org/10.1016/s0140-6736(89)92328-3))
- Salomon F, Cuneo RC, Hesp R & Sönksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *New England Journal of Medicine* 1989 **321** 1797–1803. (<https://doi.org/10.1056/NEJM198912283212605>)
- de Boer H, Blok GJ & Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocrine Reviews* 1995 **16** 63–86. (<https://doi.org/10.1210/edrv-16-1-63>)
- Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 382–395. (<https://doi.org/10.1210/jcem.83.2.4594>)
- Verhelst J & Abs R. Long-term growth hormone replacement therapy in hypopituitary adults. *Drugs* 2002 **62** 2399–2412. (<https://doi.org/10.2165/00003495-200262160-00006>)
- Rosén T & Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288. ([https://doi.org/10.1016/0140-6736\(90\)91812-o](https://doi.org/10.1016/0140-6736(90)91812-o))
- Büllow B, Hagmar L, Mikoczy Z, Nordström CH & Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clinical Endocrinology* 1997 **46** 75–81. (<https://doi.org/10.1046/j.1365-2265.1997.d01-1749.x>)
- Gilchrist FJ, Murray RD & Shalet SM. The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. *Clinical Endocrinology* 2002 **57** 363–370. (<https://doi.org/10.1046/j.1365-2265.2002.01608.x>)
- Monson JP. Long-term experience with GH replacement therapy: efficacy and safety. *European Journal of Endocrinology* 2003 **148** (Supplement 2) S9–S14. (<https://doi.org/10.1530/eje.0.148s009>)
- Götherström G, Bengtsson BA, Bosaeus I, Johannsson G & Svensson J. Ten-year GH replacement increases bone mineral density in hypopituitary patients with adult onset GH deficiency. *European Journal of Endocrinology* 2007 **156** 55–64. (<https://doi.org/10.1530/eje.1.02317>)
- Fideleff HL, Boquete HR, Stalldecker G, Giaccio AV & Sobrado PGV. Comparative results of a 4-year study on cardiovascular parameters, lipid metabolism, body composition and bone mass between untreated and treated adult growth hormone deficient patients. *Growth Hormone and IGF Research* 2008 **18** 318–324. (<https://doi.org/10.1016/j.ghir.2008.01.002>)
- Cenci MC, Conceição FL, Soars 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: Clinical and Experimental* 2008 **57** 121–129. (<https://doi.org/10.1016/j.metabol.2007.08.015>)
- Elbornsson M, Götherström G, Bosaeus I, Bengtsson BÅ, Johannsson G & Svensson J. Fifteen years of GH replacement increases bone mineral density in hypopituitary patients with adult-onset GH deficiency. *European Journal of Endocrinology* 2012 **166** 787–795. (<https://doi.org/10.1530/EJE-11-1072>)
- Feldt-Rasmussen U & Klose M. Adult growth hormone deficiency clinical management. (available at: <https://www.ncbi.nlm.nih.gov/books/NBK278943/>). Accessed on 9 July 2019.
- Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, Berinder K, Engström BE, Ekman B, Erfurth EM et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1466–1475. (<https://doi.org/10.1210/jc.2012-4059>)
- Gasco V, Prodam F, Grotto S, Marzullo P, Longobardi S, Ghigo E & Aimaretti G. Growth hormone therapy in adult growth hormone deficiency: a review of treatment schedules and the evidence for low starting doses. *European Journal of Endocrinology* 2013 **168** R55–R66. (<https://doi.org/10.1530/EJE-12-0563>)
- Elbornsson M, Götherström G, Bosaeus I, Bengtsson BÅ, Johannsson G & Svensson J. Fifteen years of GH replacement improves body composition and cardiovascular risk factors. *European Journal of Endocrinology* 2013 **168** 745–753. (<https://doi.org/10.1530/EJE-12-1083>)
- Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E & Karlsson FA. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3585–3590. (<https://doi.org/10.1210/jcem.80.12.8530603>)
- Bollerslev J, Ueland T, Jørgensen AP, Fougner KJ, Wergeland R, Schreiner T & Burman P. Positive effects of a physiological dose of GH on markers of atherogenesis: a placebo-controlled study in patients with adult-onset GH deficiency. *European Journal of Endocrinology* 2006 **154** 537–543. (<https://doi.org/10.1530/eje.1.02125>)
- Friedewald WT, Levy RI & Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry* 1972 **18** 499–502.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013 **36** (Supplement 1) S67–S74. (<https://doi.org/10.2337/dc13-S067>)
- Gutiérrez LP, Kołtowska-Häggström M, Jönsson PJ, Mattsson AF, Svensson D, Westberg B & Luger A. Registries as a tool in evidence-based medicine: example of KIMS (Pfizer International Metabolic Database). *Pharmacoeconomics and Drug Safety* 2008 **17** 90–102. (<https://doi.org/10.1002/pds.1510>)
- McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L & Wren L. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. *Quality of Life Research* 1999 **8** 373–383. (<https://doi.org/10.1023/A:1008987922774>)
- Filipsson H, Monson JP, Koltowska-Häggström M, Mattsson A & Johannsson G. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3954–3961. (<https://doi.org/10.1210/jc.2006-0524>)
- Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R & Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 3888–3921. (<https://doi.org/10.1210/jc.2016-2118>)

- 27 Feldt-Rasmussen U & Klose M. Central hypothyroidism and its role for cardiovascular risk factors in hypopituitary patients. *Endocrine* 2016 **54** 15–23. (<https://doi.org/10.1007/s12020-016-1047-x>)
- 28 Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002 **288** 321–333. (<https://doi.org/10.1001/jama.288.3.321>)
- 29 Weber MM, Biller BM, Pedersen BT, Pournara E, Christiansen JS & Höybye C. The effect of growth hormone (GH) replacement on blood glucose homeostasis in adult nondiabetic patients with GH deficiency: real-life data from the NordiNet® International Outcome Study. *Clinical Endocrinology* 2017 **86** 192–198. (<https://doi.org/10.1111/cen.13256>)
- 30 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016 **387** 1513–1530. ([https://doi.org/10.1016/S0140-6736\(16\)00618-8](https://doi.org/10.1016/S0140-6736(16)00618-8))
- 31 World Health Organization. Global report on diabetes. (available at: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf). Accessed on 9 July 2019.

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