Effects of Long-term Growth Hormone Replacement in Adults With Growth Hormone Deficiency Following Cure of Acromegaly: A KIMS Analysis

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Context: GH deficiency (GHD) may occur in adults with cured acromegaly (acroGHD).

Objective: Our objective was to examine the effectiveness and safety of GH replacement in acroGHD.

Design: This study was a retrospective analysis of data from KIMS (Pfizer International Metabolic Database).

Setting: Data were extracted from a pharmaco-epidemiological survey of >16 000 GHD adults from 31 countries.

Patients: The effectiveness population included 115 adults with acroGHD and 142 age-, gender-, and body mass index-matched GHD adults with nonfunctioning pituitary adenoma (NFPA) followed up to 5 years on GH. The safety population included 164 adults with acroGHD and 2469 with NFPA, all GH-replaced. Both acroGHD and NFPA were compared with several cohorts from the general population (including the World Health Organization Global Burden of Disease).

Outcome Measures: Outcome measures included quality of life (QoL-AGHDA), lipids, serious adverse events, and additional safety endpoints.

Results: Median GH dose was 0.3 mg/d in acroGHD and NFPA at 5 years. There were comparable improvements in QoL-AGHDA and total and low-density lipoprotein cholesterol in acroGHD and NFPA. High-density lipoprotein cholesterol increased only in acroGHD. Cardiovascular mortality was increased in acroGHD vs NFPA (standardized mortality ratio = 3.03, $P = .02$). All-cause mortality was similar in acroGHD (ratio between observed/expected cases [95% confidence interval] = 1.32 [0.70–2.25]) and lower in NFPA [observed/expected = 0.58 [0.48–0.70]) in comparison with the general population. There was no difference in incidence of all cancers, benign or malignant brain tumors, or diabetes mellitus between acroGHD and NFPA.

Conclusions: GH replacement has comparable effects on quality of life and lipids in acroGHD and NFPA. Further investigation is needed to examine whether the increased cardiovascular mortality may be attributed to the history of previous GH excess in acroGHD. (***J Clin Endocrinol Metab*** **99: 2018–2029, 2014)**

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Abbreviations: acroGHD, cured acromegaly and GHD; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; GBD, global burden of disease; GHD, GH deficiency; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IRR, incidence rate ratio; LDL, low-density lipoprotein; NFPA, clinically nonfunctioning pituitary adenoma; NS, not significant; QoL, quality of life; QoL-AGHDA, QoL-Assessment of GHD in Adults; RT, radiation therapy; SAE, serious adverse events; SDS, SD score; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

Growth hormone deficiency (GHD) in adults with hypopituitarism is associated with abnormalities in body composition, increased cardiovascular risk markers, and diminished quality of life (QoL) (1, 2). In this population, GH replacement leads to changes in body composition (decrease in visceral fat mass and increase in fat-free mass and bone mineral density [BMD]), increase in exercise capacity, decrease in several cardiovascular risk biomarkers (including serum lipids and C-reactive protein), and improvements in QoL (1, 2).

GHD has been reported in up to 70% of patients with successfully treated acromegaly secondary to surgery and/or radiation therapy (RT) (3). In this population, GHD has been associated with increased total and visceral adiposity as well as increased serum C-reactive protein levels, impaired cardiac function, and decreased QoL in comparison with those with cured acromegaly and sufficient GH secretion (4, 5).

The effects of GH replacement in GHD adults treated for acromegaly have not been thoroughly elucidated. In several studies of limited size or duration, GH replacement in patients with cured acromegaly has been shown to improve body composition, serum lipids, and QoL (6–11). On the other hand, concerns about cardiovascular safety (10) and limited beneficial effects of GH replacement (12) have also been reported. The long-term safety and efficacy of GH replacement in patients with cured acromegaly have not been well-established in a large study population.

The aim of this analysis was to study the effectiveness and safety of long-term GH replacement in adult patients with cured acromegaly and GHD (acroGHD), who were compared with patients with GHD and clinically nonfunctioning pituitary adenomas (NFPA). Patients with NFPA were chosen as controls because a population of unreplaced acroGHD patients was not available. More specifically, the KIMS (Pfizer International Metabolic Database) was queried to identify the records of adults with acroGHD.

Effectiveness outcomes were compared with a matched population of adults with GHD and NFPA. Safety was assessed in the entire population of patients with acroGHD and the entire population of adult patients with NFPA within KIMS, who met the same diagnostic criteria for GHD. Both acroGHD and NFPA were compared with several cohorts from the general population (including the World Health Organization Global Burden of Disease) and with each other.

Subjects and Methods

Subjects

The KIMS database (including over 16 000 patients from 31 countries) was searched to identify patients with cured acromegaly, meeting the following inclusion criteria: adult-onset (≥18 years) pituitary disease and stringently defined GHD (as detailed previously) (13), based on the guidelines of the GH Research Society (http://press.endocrine.org/doi/suppl/10.1210/jc.2014-1013/suppl_file/jc-2014-1013.pdf) in Supplemental Table 1 (14). These subjects were matched for age at entry into KIMS, gender, and body mass index (BMI) to patients with GHD due to NFPA, who met the same inclusion criteria.

The effectiveness population was defined as a subgroup of eligible subjects, who were either true-naive (without previous GH replacement) or semi-naive (without GH replacement for >6 months) at entry into KIMS, and received GH replacement for at least 75% of the observation period. Effectiveness was assessed at 1, 3, and 5 years on GH replacement. The safety population was defined as the entire acroGHD population, which was compared with the entire population of NFPA patients within KIMS, who were meeting the same diagnostic criteria for GHD as the effectiveness population.

Written informed consent was obtained from all study subjects at each participating center before study entry. The study was conducted according to the principles of the Declaration of Helsinki (15).

Methods

For each patient included in the analysis, data extracted from KIMS included age (at diagnosis of pituitary disease, diagnosis of GHD, and entry into KIMS), gender, cause of hypopituitarism, history of pituitary surgery or RT, presence of additional pituitary hormone deficiencies, medications, GH replacement dose, BMI, waist circumference, blood pressure (BP), body composition data (obtained by bioelectrical impedance analysis), QoL (evaluated by the QoL-Assessment of Growth Hormone Deficiency in Adults [QoL-AGHDA]) (16), peak GH response on stimulation testing, IGF-1 SD scores (SDSs) at baseline as well as on GH replacement, serum lipids, glucose, and hemoglobin A1c (HbA1c) levels, serious adverse events (SAEs), subjects' medical history (by local site investigators), and deaths. All SAEs were listed according to the MedDRA system/organ classification. In addition, prespecified safety endpoints of interest included all-cause mortality, incidence of new primary cancer (all tumor sites combined), incidence of new benign and malignant brain tumors, incidence and mortality attributed to cardiovascular and cerebrovascular diseases, and incidence of new-onset diabetes mellitus (DM). The diagnosis of DM was based on the criteria of the American Diabetes Association (17), as previously described (18). Data on pituitary tumor size at the time of diagnosis of pituitary disease were not available.

All data extracted from KIMS were provided from participating centers where patients received care. Initial doses and titration regimens for GH replacement were prescribed by clinicians in participating centers, based on local practice and KIMS recommendations advising dose titration to normal IGF-1 SDS over a 6-month period. In addition to the internal reference population (NFPA), data from external reference populations used in safety analyses included the World Health Organization (WHO) Global Burden of Disease (GBD), Cancer Incidence in Five Continents, the Kronoberg County study, the Bruneck study, the KORA S4/F4 study, the U.S. National Health Interview Survey, and the MONICA Augsburg cohort study (19–25).

Serum IGF-1 levels were centrally measured and used to calculate IGF-1 SDS as previously described (26). The following

formulae have been used to calculate IGF-1 SDS: between 1994 and 1997, IGF-1 SDS = [ln (IGF-1) − (5.95 − 0.0197 × age)]; between 1997 and 2002, IGF-1 SDS = [ln (IGF-1) − (15.92 − 0.0146 × age)/0.272]; and from 2002 onward, based on published data by Brabant et al (27).

Statistical analysis

Continuous data with skewed distributions were analyzed using Wilcoxon rank-sum test and normally distributed data using Student's *t* test. Differences between proportions were analyzed by χ^2 test or Fisher's exact test as appropriate. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated and compared between groups, using stratification for attained age and/or gender and/or country/region, depending on the level of stratification in the specific external reference. These ratios compare observed number of cases in the patient-group (O) and the expected number of cases (E). The latter number (E) quantifies the number of expected cases in the patient group if the patient group had the same specific rates as the chosen external reference population. Patient-years were calculated from date of KIMS entry or GH start date if later than KIMS entry date to date of studied event or, if no event, date of last visit or date of death. In comparisons between patient groups, incidence rate ratios (IRRs) or ratios of SMRs or SIRs were further adjusted (if not mentioned otherwise) for attained age, gender, and BMI using Poisson regression methods. In incidence analyses of malignant and benign brain tumors, data were further adjusted for history of RT and occurrence of previous malignancies. Incidence and mortality attributed to cardiovascular or cerebrovascular diseases, respectively, were adjusted for history (at study entry) of hypertension, dyslipidemia, DM, and cardiovascular disease. The 95% confidence intervals (CIs) were calculated with Byar's approximation formula or, in Poisson regression models, with likelihood ratio-based methods (28).

Statistical procedures were conducted using the Statistical Analysis System (SAS Institute, Inc). Descriptive data are expressed as median (10th percentile, 90th percentile), median (fifth percentile to 95th percentile), means ± SD, or percentages. Safety outcome measures are generally expressed as rates, ratios, and 95% CIs. *P* values <.05 were considered statistically significant.

Results

Baseline characteristics

Baseline demographic and clinical characteristics of the effectiveness and safety populations are shown in Tables 1 and 2, respectively. The diagnosis of GHD was based on the results of GH stimulation testing in 88.3% of acroGHD and 93.2% of NFPA patients. In the remainder, the diagnosis was based on the presence of low serum IGF-1 levels and multiple (≥3) pituitary hormone deficiencies. Of note, 70.4% of acroGHD and 73.8% of NFPA patients underwent insulin tolerance testing, and

Table 1. Baseline Demographic and Clinical Characteristics of the Effectiveness Population[a]

Variable	AcroGHD (n = 115)	NFPA (n = 142)	*P* Value
Gender, female/male (%)	71/44 (62/38)	79/63 (56/44)	NS
Age and duration, y			
Age at diagnosis of pituitary disease	37.9 (22.7, 54.6)	49.0 (32.8, 60.2)	.0001
Age at diagnosis of GHD	49.8 (34.1, 65.4)	52.6 (38.9, 63.3)	NS
Age at study entry	51.7 (35.7, 66.4)	53.5 (40.6, 65.8)	NS
Time from diagnosis of pituitary disease to diagnosis of GHD	9.5 (0.9, 22.0)	1.3 (0.04, 11.0)	.0001
Time from diagnosis of pituitary disease to study entry	11.8 (2.4, 27.4)	3.6 (0.6, 14.9)	.0001
Time from diagnosis of GHD to study entry	0.8 (0.1, 9.4)	0.7 (0.0, 6.4)	NS
Follow-up duration in KIMS	6.9 (0.9, 12.5)	6.4 (1.2, 12.6)	NS
Extent of hypopituitarism, n (%)			
ACTH deficiency	86 (75)	107 (75)	NS
TSH deficiency	85 (75)	107 (75)	NS
Gonadotropin deficiency	88 (77)	113 (80)	NS
Central diabetes insipidus	15 (13)	24 (17)	NS
Baseline IGF-1 SDS <−2.0	29 (40)[b]	19 (23)[b]	<.05
Treatment of pituitary tumor, n (%)			
Pituitary surgery	105 (91)	141 (99)	<.01
RT	65 (57)	49 (35)	<.001
Medical history/comorbidities, n (%)			
Visual field deficits	20 (25)[c]	80 (71)[c]	<.0001
Hypertension	28 (25)	36 (26)	NS
DM	8 (7)	5 (4)	NS
History of stroke	6 (5)	2 (1)	NS
Coronary artery disease	9 (8)	7 (5)	NS
Claudication	1 (1)	0 (0)	NS
History of tumor outside the sella	6 (5)	6 (4)	NS

[a] Data are shown as median (10th percentile, 90th percentile) or percentages as appropriate.

[b] Data were available for 72 acroGHD and 84 NFPA patients.

[c] Data were available for 81 acroGHD and 113 NFPA patients.

Table 2. Baseline Demographic and Clinical Characteristics of the Safety Population[a]

Variable	AcroGHD (n = 164)	NFPA (n = 2469)	*P* Value
Gender, female/male (%)	101/63 (62 / 38)	941/1528 (38 /62)	<.0001
Age and duration, y			
Age at diagnosis of pituitary disease	37.4 (21.2, 56.8)	47.2 (24.7, 67.2)	<.0001
Age at diagnosis of GHD	48.9 (30.2, 66.8)	51.4 (29.7, 69.7)	<.05
Age at study entry	52.9 (35.1, 69.4)	53.7 (32.8, 71.4)	NS
Time from diagnosis of pituitary disease to diagnosis of GHD	9.5 (0, 28.0)	1 (0, 18.6)	<.0001
Time from diagnosis of pituitary disease to study entry	13.1 (1.7, 30.9)	4.0 (0.3, 22.1)	<.0001
Time from diagnosis of GHD to study entry	1.4 (0, 12.7)	0.9 (0, 11.2)	<.05
Follow-up duration in KIMS	6.7 (0, 18.0)[b]	5.8 (0, 18.2)[b]	NS
Extent of hypopituitarism, n (%)			
ACTH deficiency	127 (77)	1847 (75)	NS
TSH deficiency	124 (76)	1883 (76)	NS
Gonadotropin deficiency	129 (79)	2010 (81)	NS
Central diabetes insipidus	23 (14)	456 (18)	NS
Baseline IGF-1 SDS <−2.0	31 (28)[c]	410 (29)[c]	NS
Treatment of pituitary tumor, n (%)			
Pituitary surgery	148 (90)	2273 (92)	NS
RT	95 (58)	839 (34)	<.0001
Medical history/comorbidities, n (%)			
Hypertension	35 (21)	533 (22)	NS
DM	13 (8)	201 (8)	NS
History of stroke	9 (5)	64 (3)	<.05
Coronary artery disease	13 (8)	136 (5)	NS
Claudication	2 (1)	31 (1)	NS
History of tumor outside the sella	6 (4)	89 (4)	NS

[a] Data are shown as median (5th percentile, 95th percentile) or percentages as appropriate

[b] Data are shown as median (minimum, maximum) time in years.

[c] Data were available for 109 acroGHD and 1438 NFPA patients.

39.5% of acroGHD and 40.8% of NFPA patients underwent 2 GH stimulation tests (based on local practice). Subjects were not on medical therapy for acromegaly. Most study subjects were from western European countries.

The effectiveness population comprised 115 adults with cured acromegaly (acroGHD) and 142 subjects with NFPA. There was no difference in age at diagnosis of GHD or entry into KIMS, gender distribution, and BMI between patients with acroGHD and NFPA (effectiveness population). However, subjects with acroGHD were approximately 11 years younger at the time of diagnosis of pituitary disease ($P = .0001$, Table 1) and took approximately 8 years longer than patients with NFPA to be diagnosed with GHD ($P = .0001$, Table 1). Visual field deficits were significantly less frequent among patients with acroGHD at study entry (present in 25% of patients with acroGHD and 71% of patients in the NFPA group [$P < .0001$], Table 1). In addition, patients with acroGHD were less likely than subjects with NFPA to have undergone pituitary surgery (91% of patients in the acroGHD group and 99% of patients with NFPA [$P < .01$], Table 1). In contrast, patients with acroGHD were more likely to have received sellar RT (57% of patients with acroGHD and 35% of patients in the NFPA group [$P < .001$], Table 1). The prevalence of hypertension, DM, coronary artery disease, stroke, claudication, and tumor outside the sella as well as the prevalence of ACTH, TSH, or gonadotropin deficiency was not different between the 2 groups at entry into KIMS. Most patients had 3 or more additional pituitary hormone deficiencies, including 62% of patients with acroGHD and 59% of those with NFPA (*P* value not significant]NS]). The prevalence of low (<−2) IGF-1 SDS at study entry was higher in the acroGHD group (40% of patients with acroGHD and 23% in the NFPA group [$P < .05$], Table 1), possibly reflecting the presence of a longer interval between diagnosis of pituitary disease and GHD in the acroGHD population or perhaps more conservative selection of patients for inclusion in the acroGHD group by treating clinicians.

The safety population comprised 164 adults with acroGHD and 2469 adults with NFPA. Baseline findings in the safety population (Table 2) broadly mirrored those in the effectiveness population. However, the acroGHD group had a higher proportion of women (62%) in comparison with the NFPA (38%) group ($P < .0001$). At study entry, 5% of patients with acroGHD and 3% of those with NFPA had a history of stroke ($P < .05$).

Long-term treatment effectiveness

Data on vital, anthropometric, QoL, and laboratory tests in the effectiveness population during the study pe-

Table 3. Anthropometric, QoL, and Laboratory Data During the Study Period (Effectiveness Population)[a]

	Study Entry			Year 1			Year 3			Year 5		
Variable	AcroGHD	NFPA	*P* Value (Baseline Between Groups)	AcroGHD	NFPA	*P* Values[b] Within Groups: AcroGHD NFPA	AcroGHD	NFPA	*P* Values[b] Within Groups: AcroGHD NFPA	AcroGHD	NFPA	*P* Values[b] Within Groups: AcroGHD NFPA
GH dose, mg/d												
Median	0.2	0.2	NS	0.4	0.3	.0001	0.4	0.4	.0001	0.3	0.3	.0001
10th, 90th centile	0, 0.4	0, 0.3		0.1, 0.6	0.2, 0.6	.0001	0.2, 0.7	0.2, 0.6	.0001	0.2, 0.7	0.2, 0.6	.0001
n	115	142		99	123		88	108		69	81	
IGF-1 SDS												
Median	−1.6	−1.2	NS	0.6	0.7	.0001	0.8	0.7	.0001	0.8	1.0	.0001
10th, 90th centile	−4.4, 0.7	−2.9, 0.4		−1.7, 2.1	−1.2, 2.1	.0001	−0.6, 2.1	−0.9, 1.8	.0001	−1.8, 1.8	−0.2, 1.8	.0001
n	72	84		67	77		62	86		41	53	
BMI, kg/m^2												
Median	28.5	27.7	NS	29.9	27.9	NS	28.8	28.0	NS	29.3	28.4	NS
10th, 90th centile	23.6, 37.5	24.5, 34.9		23.8, 39.0	24.3, 34.2	NS	23.2, 38.7	23.9, 35.2	NS	22.9, 38.8	24.3, 36.3	.002
n	109	142		75	92		77	99		63	74	
Waist circumference, cm												
Median	101	97	NS	97	95	NS	98	95	NS	103[e]	93[e]	.0075
10th, 90th centile	82, 118	85, 113		79, 117	82, 107	.0011	79, 118	81, 110	NS	82, 121	84, 109	NS
n	89	108		67	81		69	89		49	61	
Systolic BP, mm Hg												
Median	130	130	NS	124[c]	131[c]	.012	128	130	NS	129	129	NS
10th, 90th centile	110, 161	111, 155		110, 150	115, 155	NS	110, 151	110, 163	NS	110, 150	110, 155	NS
n	110	135		82	92		80	100		62	75	
Diastolic BP, mm Hg												
Median	80	80	NS	80	80	.011	80	80	NS	80	80	NS
10th, 90th centile	70, 100	70, 92		70, 90	70, 91	NS	64, 92	70, 100	NS	70, 93	70, 95	NS
n	110	135		82	91		80	100		62	75	
Fat-free mass. kg												
Median	53.4	55.9	NS	62.0	59.5	NS	59.5	53.7	NS	64.9	50.8	NS
10th, 90th centile	41.4, 78.8	41.5, 71.6		42.9, 83.6	44.8, 72.1	NS	43.6, 86.3	42.0, 71.1	.033	41.0, 78.6	41.3, 77.3	NS
n	39	53		30	35		30	45		17	31	
Fat mass, kg												
Median	28.2	25.2	.037	28.4	23.4	NS	30.2	24	NS	36.2	24.8	NS
10th, 90th centile	16.2, 47.0	14.4, 37.5		16.9, 52.5	16.1, 35.9	NS	17.9, 52.8	15.8, 40.7	NS	16.3, 59.5	18.7, 34.7	NS
n	39	53		30	35		30	45		18	31	
QoL-AGHDA score												
Median	13	12	NS	5	3	.0001	6	4	.0001	5	4	.0001
10th, 90th centile	3, 21	0, 22		0, 17	0. 13	.0001	0, 20	0, 18	.0001	0, 19	0, 18	.017
n	85	99		61	68		63	86		46	53	
Total cholesterol, mmol/L												
Median	5.6	5.8	.026	5.5	5.7	NS	5.5	5.5	NS	5.0	5.2	.0005
10th, 90th centile	4.4, 7.0	4.7, 7.4		4.6, 7.2	3.9, 7.2	.045	4.3, 6.9	3.9, 6.8	.001	4.0, 6.5	3.7, 6.6	.0021
n	69	76		55	70		58	84		41	51	
LDL cholesterol, mmol/L												
Median	3.3	3.7	.015	3.2	3.6	NS	3.2[d]	3.2[d]	NS	2.7	3.0	.0003
10th, 90th centile	2.2, 4.6	2.5, 5.3		2.5, 4.7	2.1, 4.7	.0088	2.4, 4.5	2.0, 4.4	.0001	1.9, 4.3	2.0, 4.4	.0001
n	65	72		51	68		57	82		40	51	
HDL cholesterol, mmol/L												
Median	1.2	1.3	NS	1.2	1.2	NS	1.4	1.2	NS	1.3	1.2	.045
10th, 90th centile	0.7, 1.9	0.8, 1.8		0.8, 2.0	0.8, 1.7	NS	0.9, 2.0	0.8, 1.9	NS	0.9, 1.8	0.9, 1.8	NS
n	69	76		55	70		58	84		41	51	
Triglycerides, mmol/L												
Median	1.7	1.8	NS	1.8	1.9	NS	2.0	1.8	NS	1.8	1.6	NS
10th, 90th centile	0.9, 3.6	0.9, 3.7		0.9, 3.8	1.0, 3.3		1.0, 3.6	1.0, 3.3		1.0, 3.5	1.1, 3.2	NS
n	69	76		55	70	NS	58	84	NS	41	51	
Fasting glucose, mmol/L												
Median	4.8	4.6	NS	5.0	4.9	.0001	5.1	5.0	.0013	5.1	5.1	.0001
10th, 90th centile	4.1, 6.2	3.9, 5.7		4.4, 7.0	4.2, 5.9	.0027	4.2, 6.4	4.4, 5.7	.0001	4.4, 7.1	4.4, 6.0	.0011
n	64	78		51	44		50	58		35	46	
HbA1c, %												
Median	5.3	5.2	NS	5.3	5.3	.010	5.4	5.3	.037	5.4	5.4	.019
10th, 90th centile	4.3, 6.0	4.5, 6.0		4.5, 6.3	4.4, 5.9	.023	4.5, 6.5	4.5, 6.2	NS	4.4, 6.6	4.5, 6.2	.067
n	77	86		62	71		64	81		48	61	

[a] To convert quantities from SI to conventional units, the following conversion factors can be used: cholesterol (mg/dL) = cholesterol (mmol/L) divided by 0.0259; glucose (mg/dL) = glucose (mmol/L) divided by 0.0555; triglycerides (mg/dL) = triglycerides (mmol/L) divided by 0.0113.

[b] *P* values shown pertain to change from baseline within each group. Unless otherwise indicated, between group comparisons were NS.

[c] $P = .014$ for the difference between changes from baseline (between groups).

[d] $P = .030$ for the difference between changes from baseline (between groups).

[e] $P = .038$ for the difference between changes from baseline (between groups).

riod are shown in Table 3 as well as Supplemental Figures 1 and 2 and Figure 1. At study entry, patients with acroGHD had higher total fat mass ($P = .037$) and lower total cholesterol ($P = .026$) and low-density lipoprotein (LDL) cholesterol ($P = .015$) concentrations than those with NFPA. At entry into KIMS, 15 of 115 patients (13%) with acroGHD and 19 of 142 patients (13%) with NFPA were taking lipid-lowering medications (P = NS between groups). At baseline, there was no significant difference in median IGF-1 SDS, starting GH dose, BMI, waist circumference, systolic and diastolic BP, fat-free mass, QoL-AGHDA scores, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose, and HbA1c between the 2 groups (Table 3).

The median GH dose was 0.3 mg daily in both groups (acroGHD and NFPA) at the end of the observation period

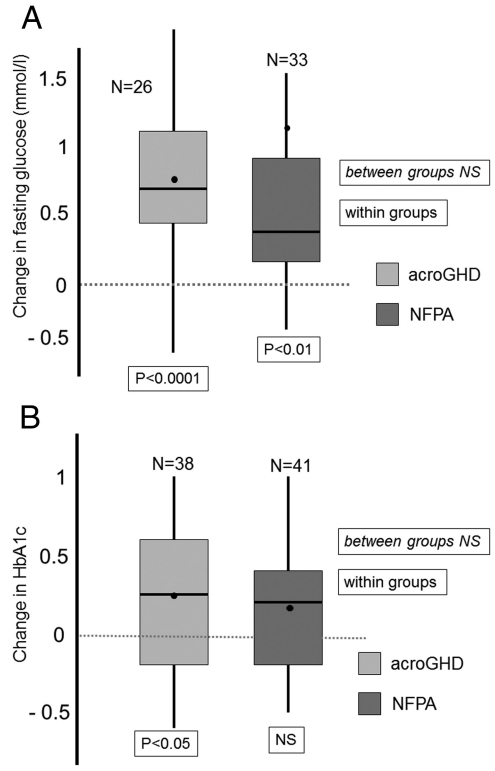

Figure 1. Change in fasting plasma glucose (A) and HbA1c (B) in patients with acroGHD and NFPA after 5 years of GH replacement. A, There was an increase in plasma glucose in both groups from 4.8 (4.1, 6.2) mmol/L (86 [74, 112] mg/dL) at baseline to 5.1 (4.4, 7.1) mmol/L (92 [79, 128] mg/dL) at 5 years in acroGHD ($P = .0001$ within group) and from 4.6 (3.9, 5.7) mmol/L (83 [70, 103] mg/L) at baseline to 5.1 (4.4, 6.0) mmol/L (92 [79, 108] mg/dL) at 5 years in NFPA ($P = .0022$ within group; P = NS between groups). B, There was a rise in HbA1c only in the acroGHD group by the end of the study from 5.3% (4.3%, 6.0%) at baseline to 5.4% (4.4%, 6.6%) at 5 years in acroGHD ($P = .019$ within group) and from 5.2% (4.5%, 6.0%) at baseline to 5.4% (4.5%, 6.2%) at 5 years in NFPA ($P = .067$ within group; P = NS between groups). All data shown pertain to the effectiveness population. To convert quantities from SI to conventional units, the following conversion factors can be used: glucose (mg/dL) = glucose (mmol/L) divided by 0.0555.

(5 years), and IGF-1 SDS similarly increased during this time (P = NS between groups, Supplemental Figure 1, a and b). There were comparable, sustained improvements in QoL in both groups at 5 years (Supplemental Figure 1c).

By the end of the study period, there were comparable between-group decreases in total and LDL cholesterol at 5 years in acroGHD and NFPA (P = NS between groups, Supplemental Figure 2, a and b). Of note, HDL cholesterol increased only in the acroGHD group (Supplemental Figure 2c). At the end of the study, 25 of 115 subjects (22%) with acroGHD and 35 of 142 patients (25%) with NFPA were taking lipid-lowering medications (P = NS between groups). After excluding patients on lipid-lowering medications, there were comparable decreases in total and LDL cholesterol between groups (data not shown). There was a comparable increase in plasma glucose in both groups (P = NS between groups, Figure 1A). There was a rise in HbA1c only in the acroGHD group by the end of the study ($P = .019$, Figure 1b).

Safety

Crude incidence rates and rate ratios (IRRs) of SAEs in the safety population are shown in Table 4. When all SAEs were considered, the IRR between acroGHD and NFPA was higher for the following categories: hepatobiliary, musculoskeletal, and procedures. In contrast, the IRR was lower for all (new and recurrent) neoplasms combined (this finding was no longer significant after excluding 163 recurrent pituitary adenomas in the NFPA group).

When only GH-related SAEs (based on site investigators' opinion) were considered, the IRR between acroGHD and NFPA was higher only for musculoskeletal conditions, albeit with a small number of events. The IRR was lower for all (new and recurrent) neoplasms combined (again, this finding was no longer significant after excluding 71 recurrent pituitary adenomas in the NFPA group).

Data on prespecified safety endpoints are shown in Table 5 and Figure 2. All-cause mortality in the acroGHD group was similar to the general population (19) and lower in the NFPA group, yielding an elevated ratio between SMRs for acroGHD over NFPA. Using Poisson regression, the association between study group (acroGHD vs. NFPA) and all-cause mortality was of marginal statistical significance (SMR = 1.88; 95% CI = 1.0–3.4; $P = .05$). All-cause mortality rates increased by attained age (on average, 7.4% per year [5.5%–9.3%], $P < .0001$), but this increase was lower compared with the corresponding normal population rates (on average, SMR decreased by 2.1% per year of attained age [95% CI, −0.4% to −3.7%, $P = .015$]). There was a slightly higher relative mortality noted in women (SMR for women vs. men = 1.51 [1.02–2.22], $P = .04$).

Table 4. SAEs in the Safety Population, Including All SAEs and Those Considered to be GH-related According to Local Site Investigators' Opinion (Without Central Adjudication)

	All SAEs				GH-related SAEs			
Type of Disorder (MedDRA SOC Category)	**SAEs AcroGHD**	**SAEs NFPA**	**IRR[a]**	**95% CI**	**SAEs AcroGHD**	**SAEs NFPA**	**IRR[a]**	**95% CI**
Blood and lymphatic	0	7	0	NA	0	0	NA	NA
Cardiac	7	94	1.01	0.47–2.18	1	4	3.39	0.38–30.37
Congenital, familial or genetic	0	3	0	NA	0	0	NA	NA
Ear and labyrinth	1	11	1.23	0.16–9.56	0	0	NA	NA
Endocrine	5	43	1.58	0.63–3.99	1	5	2.72	0.32–23.24
Eye	0	15	0	NA	0	2	0	NA
Gastrointestinal	4	70	0.78	0.28–2.13	0	2	0	NA
General/administration sites	10	79	1.72	0.89–3.32	1	6	2.26	0.27–18.8
Hepatobiliary	5	22	3.09	1.17–8.15	0	1	0	NA
Immune	0	2	0	NA	0	0	NA	NA
Infections	13	173	1.02	0.58–1.79	1	2	6.79	0.62–74.87
Injury and poisoning	3	84	0.48	0.15–1.53	0	3	0	NA
Investigations	2	39	0.70	0.17–2.88	0	4	0	NA
Metabolic and nutrition	5	40	1.70	0.67–4.30	1	15	0.91	0.12–6.85
Musculoskeletal	10	65	2.09	1.07–4.06	2	1	27.15	2.46–299.5
Neoplasms (all)[b]	12	389	0.42	0.24–0.74	3	140	0.29	0.09–0.91
Nervous system	13	160	1.10	0.63–1.94	1	12	1.13	0.15–8.70
Pregnancy	1	6	2.26	0.27–18.8	0	0	NA	NA
Psychiatric	0	27	0	NA	0	2	0	NA
Renal and urinary	3	22	1.85	0.55–6.19	0	1	0	NA
Reproductive and breast	1	27	0.50	0.07–3.70	0	1	0	NA
Respiratory	3	32	1.27	0.39–4.16	0	1	0	NA
Skin	0	7	0	NA	0	1	0	NA
Surgical and medical procedures	23	149	2.10	1.35–3.25	0	8	0	NA
Vascular	4	42	1.29	0.46–3.61	1	3	4.53	0.47–43.51
Total	125	1608	NA	NA	12[c]	214	NA	NA

Abbreviations: NA, not applicable; SOC, system organ class.

[a] IRRs were calculated using NFPA as the reference population.

[b] Includes both new and recurrent neoplasms (both benign and malignant).

[c] GH-related SAEs in the acroGHD group include 1 case of supraventricular arrhythmia, 1 case of acute adrenal crisis, 1 patient with peripheral edema, 1 patient with a tooth infection, 1 patient with type 2 DM, 1 patient with arthralgia, 1 patient with osteoarthritis, 1 case of colon cancer, 1 case of meningioma, 1 patient with ovarian cancer, 1 patient with seizure, and 1 patient with hypotension.

Cardiovascular mortality was increased in the acroGHD group in comparison with the general population (19). In contrast, cardiovascular mortality was decreased in patients with NFPA in comparison with the general population, yielding an elevated ratio between SMRs for acroGHD over NFPA. On Poisson regression analysis, predictors of cardiovascular mortality were patient group (acroGHD vs NFPA, $P = .0199$), younger attained age ($P = .0016$), female gender ($P = .0344$), and history of cardiovascular disease ($P = .0001$). The SMR between acroGHD over NFPA remained elevated on Poisson regression (SMR = 3.03 [1.31–6.97], $P = .0092$), and did not significantly change after excluding patients with a history of cardiovascular or cerebrovascular disease at KIMS entry (data not shown).

There was no difference in cerebrovascular mortality between acroGHD or NFPA, examined in comparison with the general population and between each other (19). Similarly, there was no significant difference in incidence rates for cardiovascular or cerebrovascular disease between acroGHD and NFPA.

There was no difference between the 2 groups with regard to incident new cancers (all sites combined) in comparison with the general population or benign brain tumors (20). However, the incidence of malignant brain tumors was increased in both acroGHD and NFPA in comparison with the external reference population (Table 5) (20). Of note, the corresponding ratio between SIRs for acroGHD over NFPA was not elevated (Table 5).

The SIR for malignant brain tumors in patients with a history of RT was 6.07 (1.96–14.17) vs 3.32 (0.89–8.49) in those without a history of RT. However, this difference in SIRs between patients with previous RT and those without RT was not statistically significant (neither crudely nor after control for attained age, gender, and previous history of malignancy ($P = .34$).

The incidence of DM was increased in both acroGHD and NFPA groups in comparison with most external ref-

Table 5. Safety Analysis in the Entire (Safety) Population

	AcroGHD (n = 164)				NFPA (n = 2469)					
Endpoint	Events[b]	Crude Rate (per 1000 Person-Years)[b]	O/E	95% CI	Events[b]	Crude Rate (per 1000 Person-Years)[b]	O/E	95% CI	SMR or SIR (95% CI)[a]	*P* Value
All-cause mortality	13[c]	11.24	1.32	0.70–2.25	114[c]	7.26	0.58	0.48–0.70	1.88 (1.04–3.38)	.0357
Cardiovascular mortality	7	6.13	2.89	1.16–5.92	36	2.29	0.68	0.48–0.94	4.23 (1.89–9.47)	.0004
Cerebrovascular mortality	1	1.02	1.60	0.05–7.95	14	0.91	0.96	0.53–1.60	1.67 (0.26–10.86)	NS
Incidence of all cancers	10	8.78	1.05	0.50–1.93	153	9.99	1.05	0.89–1.23	0.96 (0.50–1.84)	NS
Incidence of malignant brain tumors	2	1.76	15.80	1.77–57.05	7	0.46	3.68	1.47–7.58	3.04 (0.62–14.98)	NS
Incidence of benign brain tumors	2	1.75	NA	0.44–6.98	7	0.45	NA	0.21–0.94	3.90 (0.81–18.78)[d]	NS
Incidence of cardiovascular disease	10	8.90	NA	4.79–16.55	110	7.25	NA	6.01–8.74	1.23 (0.64–2.35)[d]	NS
Incidence of cerebrovascular disease	7	6.23	NA	2.97–13.07	66	4.35	NA	3.42–5.53	1.43 (0.66–3.12)[d]	NS
Incidence of DM[e]	19	19.42	3.84[f]	2.31–5.99	289	21.55	3.86[f]	3.43–4.33	0.92 (0.58–1.47)	NS

Abbreviations: NA, not applicable; O/E, observed/expected case ratio.

[a] Denotes estimate of the crude ratio between SMR (or SIR) for acroGHD over NFPA patients (unless otherwise stated).

[b] The number of patient-years ranged between 978 and 1156 in the acroGHD group, whereas the number of patient-years ranged between 13 408 and 15 701 in the NFPA group. To calculate the number of patient-years for each endpoint, divide the number of events by the corresponding crude rate (divided by 1000).

[c] In the acroGHD group, causes of death were as follows: cardiovascular, 6 (46%) (including myocardial infarction [3 cases], heart failure [2 cases], and sudden death [1 case]); malignancies, 3 (23%); cerebrovascular, 1 (8%); infectious, 1 (8%); unknown, 2 (15%). In the NFPA group, causes of death were as follows: malignancies, 31 (27%); cardiovascular, 30 (26%); infectious, 13 (11%); cerebrovascular, 12 (11%); respiratory, 3 (3%); neuropsychiatric, 3 (3%); benign tumors, 1 (1%); digestive, 1 (1%); endocrine, 1 (1%); unknown, 19 (16%). Deaths from unknown causes were distributed proportionately within groups before calculating cause-specific mortality.

[d] Denotes estimate of the crude IRR (with 95% CI).

[e] Patients with DM at KIMS entry were excluded from this analysis.

[f] Data from the Kronoberg County (Sweden) were used as external reference (as noted in Subjects and Methods) (21).

erence populations (Supplemental Table 2) (21–25). However, the ratio between SIRs for acroGHD over NFPA was not elevated (Tables 4 and 5). Using Poisson regression, a higher BMI predicted a higher incidence of DM ($P < .0001$).

Discussion

The goals of the present study were to investigate the effectiveness and safety of GH replacement in adults with GHD and a history of cured acromegaly, a condition that occurs in most patients successfully and definitively treated for acromegaly, according to most (3, 29, 30), but not all (31), studies. Because a group of hypopituitary patients with a history of acromegaly and no GH replacement was not available, acromegalic patients with GHD were compared with a group of adults with hypopituitarism due to NFPA, who also received physiologic GH replacement. In safety analyses, both acroGHD and NFPA were compared with several cohorts from the general population and with each other.

In response to GH replacement therapy, there were comparable increases in IGF-1 SDS between the 2 patient groups, the vast majority achieving physiologic IGF-1 SDS. There were comparable, significant, and sustained improvements in QoL scores in both groups, supporting the hypothesis that GH replacement likely has beneficial effects on QoL of patients with acroGHD, similar to those observed in studies of patients with GHD of other etiologies in most (32–36), but not all (37), studies.

In addition, serum lipids, including total and LDL cholesterol, decreased and HDL cholesterol increased in patients with acroGHD by the end of the study period. Quantitatively similar effects (with regard to total and LDL cholesterol) were noted in patients with NFPA after 5 years of GH replacement. However, improvements in serum lipids were noted earlier in the NFPA group, possibly related to these patients' higher baseline total and LDL cholesterol levels (38). It may be noted that these presum-

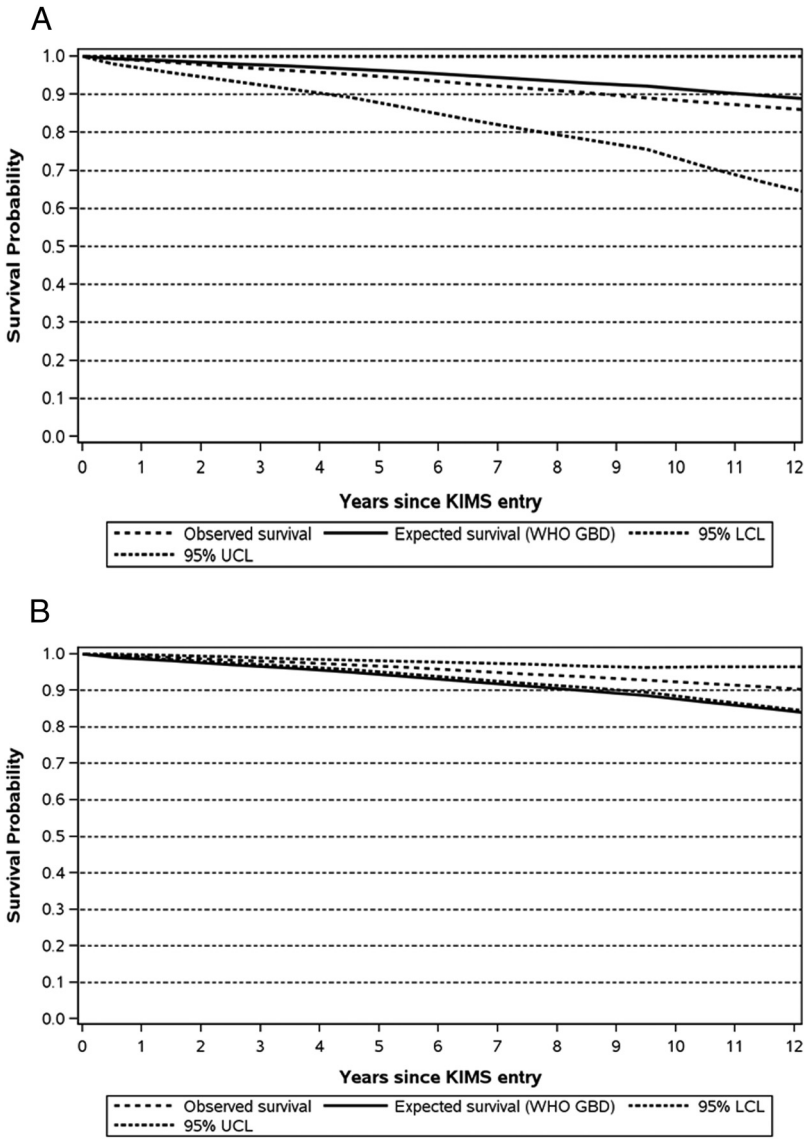

Figure 2. Survival in patients with acroGHD (A) and NFPA (B) since study entry in comparison with an external reference population (WHO GBD data as detailed under Subjects and Methods) (19). Patient-years (and expected mortality rates) for all-cause mortality analyses were stratified on attained age, gender, and country/region. All data shown pertain to the safety population (95% CIs included). Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.

ably beneficial effects on serum lipids occurred without any significant change in BMI or body adiposity, supporting the hypothesis that GH replacement directly influences lipoprotein kinetics (1, 14, 39). The effects of GH replacement on serum lipids were comparable to those in GHD adults without a history of acromegaly (40, 41). Overall, there were minor increases in fasting glucose and HbA1c levels during the study, which were comparable between the 2 patient groups, likely reflecting effects of GH replacement raising insulin resistance (1, 14, 40, 41).

Safety considerations are particularly important in studies of patients with acromegaly, because patients with active disease have increased cardiovascular mortality (42).We found no difference in the incidence for cardiovascular or cerebrovascular disease between acroGHD and NFPA. In the present study, all-cause mortality was not increased in acroGHD above that of the external reference population. However, the ratio between SMRs for acroGHD over NFPA was elevated, likely as a result of decreased all-cause mortality in the NFPA group in comparison with the external reference population. Previous studies have suggested an increase in all-cause mortality in hypopituitary patients, particularly in women (43–45). Although the explanation for the lower mortality in the NFPA group in the present study is not clear, this finding is nevertheless reassuring.

In the present study, cardiovascular mortality was increased in the acroGHD group in comparison with the external (WHO GBD) and internal (NFPA) reference populations. Patients with acromegaly are at increased risk of cardiovascular morbidity and mortality (as well as additional systemic and metabolic comorbidities), reflecting cumulative exposure to GH excess (46–48). It is not known whether patients with cured acromegaly and unreplaced GHD remain at higher risk of cardiovascular mortality. Whether excess cardiovascular mortality may be attributed to the history of previous GH excess in the acroGHD group cannot be determined based on the findings of the present study, which did not include a control population of unreplaced, GHD acromegalic patients in remission. Nevertheless, the present findings suggest that patients with acroGHD on GH replacement be carefully monitored for their cardiovascular health.

Reassuringly, the incidence of all cancers combined was not elevated in acroGHD or NFPA patients. However, the incidence of malignant brain tumors was similarly increased in both groups in comparison with the external reference population (without a higher risk in acroGHD in comparison with NFPA). Of note, large studies of GH-replaced children and adults have not reported an increased risk of brain malignancies or recurrent or second-

ary tumors in these populations (49, 50). On stratification analysis in the present study, the incidence of malignant brain tumors was elevated only in patients with previous RT, which is a known risk factor for brain tumors (51, 52). These observations raise the possibility that previous RT contributed to the increased incidence of malignant brain tumors in the present study. However, RT was not an independent predictor of incident malignant tumors on multivariate regression, suggesting that further study is needed to clarify this issue.

The present study findings are consistent with a BMI-dependent increase in risk of incident DM in GHD patients receiving replacement therapy and are in broad agreement with previous studies (18, 53). However, this risk was not higher in patients with acroGHD compared with those with NFPA. It may also be noted that unreplaced GHD is associated with increased risk of prevalent DM, related to the presence of adverse body composition and insulin resistance (54).

Strengths of the present study include its large population size, stringent definition of GHD, carefully matched NFPA group (effectiveness population), use of several cohorts as control groups (safety analyses), and long duration of follow-up. Despite the potential limitations of GH stimulation testing in patients with acromegaly, it may be noted that the frequent use of RT and the high prevalence of multiple additional pituitary hormone deficiencies and low baseline IGF-1 SDS all corroborate the presence of GHD in the study population.

Limitations of this study include its retrospective design, which restricts available data to those recorded in the database. As a corollary, data on BMD, cardiac function, serum biomarkers of systemic inflammation or endothelial function, and exercise capacity were not available. In addition, data on body composition were limited to a subset of the patient population. There were low numbers of events in some safety analyses, leading to wide CIs. By virtue of design of this observational pharmaco-epidemiologic survey, there were no uniform practices for implementation and assessment of GH replacement among clinical centers, allowing for a potential selection bias into therapy that may have been different for the 2 groups. However, the study captures meaningful data from real-world clinical practice over a considerable period of time. It may also be argued that conducting a large, lengthy, placebo-controlled clinical trial of GH replacement in patients with acroGHD may not be feasible in countries where GH replacement is available for use in GHD adults.

In conclusion, the present findings suggest that GH replacement has beneficial effects on QoL and serum lipids in patients with acroGHD, comparable to those with NFPA. With the exception of elevated cardiovascular mortality, safety analyses suggested comparable safety profile in patients with acroGHD and NFPA receiving GH replacement. Further investigation is needed to examine whether the increased cardiovascular mortality can be attributed to the history of previous GH excess in acroGHD. Inclusion of a control group of unreplaced acroGHD subjects in future studies would likely be helpful to clarify the effect of GH replacement on cardiovascular outcomes in this population.

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