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Clinical Research Article

Long-term Safety of Growth Hormone in Adults With Growth Hormone Deficiency: Overview of 15 809 GH-Treated Patients

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Abstract

Context: Data on long-term safety of growth hormone (GH) replacement in adults with GH deficiency (GHD) are needed.

Objective: We aimed to evaluate the safety of GH in the full KIMS (Pfizer International Metabolic Database) cohort.

Methods: The worldwide, observational KIMS study included adults and adolescents with confirmed GHD. Patients were treated with GH (Genotropin [somatropin]; Pfizer, NY) and followed through routine clinical practice. Adverse events (AEs) and clinical characteristics (eg, lipid profile, glucose) were collected.

Results: A cohort of 15 809 GH-treated patients were analyzed (mean follow-up of 5.3 years). AEs were reported in 51.2% of patients (treatment-related in 18.8%). Crude AE rate was higher in patients who were older, had GHD due to pituitary/hypothalamic tumors, or adult-onset GHD. AE rate analysis adjusted for age, gender, etiology, and follow-up time showed no correlation with GH dose. A total of 606 deaths (3.8%) were reported (146 by neoplasms, 71 by cardiac/vascular disorders, 48 by cerebrovascular disorders). Overall, de novo cancer incidence was comparable to that in the general population (standard incidence ratio 0.92; 95% CI, 0.83-1.01). De novo cancer risk was significantly lower in patients with idiopathic/congenital GHD (0.64; 0.43-0.91), but similar in those with pituitary/hypothalamic tumors or other etiologies versus the general population. Neither adult-onset nor childhood-onset GHD was associated with increased de novo cancer risks. Neutral effects were observed in lipids/fasting blood glucose levels.

Conclusion: These final KIMS cohort data support the safety of long-term GH replacement in adults with GHD as prescribed in routine clinical practice.

Key Words: adult growth hormone deficiency, growth hormone, hypopituitarism, cancer, safety, KIMS

Abbreviations: AE, adverse event; AO-GHD, adult-onset growth hormone deficiency; BMI, body mass index; BP, blood pressure; CO-GHD, childhood-onset growth hormone deficiency; GH, growth hormone; GHD, growth hormone deficiency; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; KIMS, Pfizer International Metabolic Database; LDL, low-density lipoprotein; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term (MedDRA); SAE, serious adverse event; SDS, standard deviation score; SIR, standardized incidence ratio; WHO, World Health Organization.

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Growth hormone deficiency (GHD) observed in adults either presents in childhood and persists into adulthood (childhood-onset GHD [CO-GHD]) or arises in adulthood (adult-onset GHD [AO-GHD]). Based on postmarketing surveillance studies, GHD in adults is most frequently caused by hypothalamic/pituitary lesions (1, 2), often due to a pituitary adenoma or its associated treatments by surgery or radiotherapy (3). Adult GHD is linked to a wide spectrum of clinical features, including abnormal body composition, reduced bone mineral density, decreased muscle strength and exercise capacity, unfavorable metabolic profile, and impaired physiological well-being and quality of life (3-6). As symptoms of GHD in adults are nonspecific and secretion of growth hormone (GH) is pulsatile, biochemical tests measuring peak GH levels in response to GH simulation are usually needed to confirm GHD (3, 5). Data from some studies also suggest that hypopituitary patients with untreated GHD may be predisposed to decreased life expectancy due to cardiovascular and cerebrovascular diseases (7, 8), although an association between GHD and increased mortality has not been definitively proven (6).

Since recombinant human GH was first introduced in the mid-1980s, clinical studies have shown that GH therapy increased lean body mass and decreased body fat (9, 10), improved bone health (11), enhanced patient-reported quality of life (12), and reduced total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol (10, 13, 14) in adults with GHD, although its effects on cardiovascular risks and mortality have been inconclusive (10, 14-16). Administration of long-term GH replacement in adults with GHD is overall well-tolerated (17, 18), but concerns regarding potential risks of diabetes mellitus, new malignancy, tumor recurrence, and cardiovascular diseases still remain. Long-term surveillance studies of large cohorts and adequate controls are therefore needed for a better benefit-risk assessment (10, 16).

KIMS (Pfizer International Metabolic Database), established in 1994, was an international, multicenter, noninterventional, open-label database of long-term clinical and safety outcomes of GH replacement (Genotropin [somatropin]; Pfizer, New York) in adult and adolescent hypopituitary patients with GHD, as prescribed by physicians in routine clinical practice. The real-world clinical setting of KIMS allows for collection of data complementary to those from randomized clinical trials, which often have limited numbers and characteristics of enrolled patients, and relatively short durations of treatment and follow-up. Data from KIMS have revealed improvements in body composition, lipid profile, and quality of life with GH replacement, and the favorable effects were maintained with long-term administration of GH (19-24). KIMS concluded in 2012 with a total of 15 809 GHD patients who received GH replacement therapy. With the availability of data from the full cohort of GHD patients, we aimed to evaluate the overall safety outcomes of GH-treated patients (n = 15 809) during their follow-up for a maximum of 18.3 years in KIMS until the database was discontinued.

Materials and Methods

Study Design and Patients

Enrolled patients included hypopituitary adults and adolescents with confirmed GHD and closed epiphyses who were prescribed GH (Genotropin [somatropin]; Pfizer, New York). GHD was diagnosed by a variety of GH stimulation tests as previously described (1), following established criteria (25, 26). Patients transitioning from pediatric to adult care were also enrolled. Participation in any interventional clinical trial during KIMS was not permitted. Written informed consent was obtained from all participants. Patients were treated and followed by the KIMS investigators according to standards and judgment of clinical practice. No prespecified endpoints were defined in the study. Relevant data were collected during the course of normal clinical practice.

Safety and Treatment Outcomes

Safety outcomes included all reported adverse events (AEs) and serious adverse events (SAEs), regardless of causality. Events of drug withdrawal (temporary, permanent, or dose reduction), study discontinuation, and death were recorded, and their possible causes were assessed. AEs, SAEs, and causes of death were classified according to system organ class (SOC) and preferred term (PT) defined by the Medical Dictionary for Regulatory Activities (MedDRA). Metabolic variables such as the lipid profile and glucose were monitored. Clinical characteristics (eg, height, weight, blood pressure [BP], waist and hip circumferences, insulin-like growth factor-1 [IGF-1], lipid profile) were assessed as treatment outcomes.

Statistics

Data from all patients who received ≥ 1 dose of GH in KIMS were analyzed. Analyses were based on all available data. Missing values were assumed to be missing completely at random and were not imputed. For any variables with missing data, the denominator was based on the total number of patients with available data. Baseline demographics were summarized by descriptive statistics. Observed crude incidence rates of AEs and SAEs per 1000 patient-years were compared among different subgroups by gender, age at KIMS start, GHD etiology, GHD onset, prior radiation therapy at KIMS start, mean IGF-1 standard deviation score (SDS) in KIMS (between first and last visits), and mean daily GH dose in KIMS (between first and last visits), using Poisson regression methods with 95% two-sided CIs calculated with likelihood-based methods. Dose effects on AEs were further analyzed by duration of follow-up and adjusted for age, gender, and GHD etiology. Study discontinuations and deaths were summarized for the full cohort and by gender, age at KIMS start, and GHD etiology. Vital signs, IGF-1 SDS, fasting glucose concentrations, and lipids were descriptively analyzed at baseline and yearly during follow-up.

Incidence of de novo cancer was calculated for patients without a prior history of cancer at KIMS start. Patients with missing information on birth date or gender were excluded from the analysis. Standardized incidence ratios (SIRs) for all-site cancers and individual cancer types of interest were computed as the ratio of observed number of cases in KIMS to the expected number of cases based on incidence rates in the general population according to the World Health Organization (WHO) IARC database (27-30). The 95% two-sided CIs were calculated with the Byar approximation. Other nonmelanoma skin cancers (ICD-10 C44) were excluded from SIR calculations as they are inconsistently reported in different cancer registries of the WHO IARC database. Stratification was performed by gender, attained age, calendar time period, and country. Overall cancer SIR

and those for subgroups by age at KIMS start, GHD etiology, GHD onset, GH treatment prior to study entry, mean GH dose, mean IGF-1 SDS, and time interval during KIMS follow-up are presented. *P*-values < 0.05 were considered statistically significant and a two-sided significance level was applied.

Results

Demographics of Participants

A total of 15 809 patients were recruited from 800 centers in 31 countries across 5 continents and received GH replacement therapy in KIMS, with Germany and the United Kingdom having the highest number of participants (19.8% and 19.2%, respectively). Approximately half of the patients were male (50.5%), and the majority (94.4%) were Caucasian (Table 1). At KIMS start, 28.6% of patients were receiving GH (non-naïve), 13.8% had not been receiving GH therapy for ≥ 6 months (semi-naïve), and 57.6% had never received GH therapy (naïve). Most patients (77.4%) had AO-GHD, while 22.2% had CO-GHD. The mean age at KIMS start was 43.9 years, similar in males and females (44.0 and 43.8 years, respectively). Age distributions at KIMS start and GHD diagnosis were not gender-related (Fig. 1). The most common etiology of GHD was a pituitary/hypothalamic tumor (59.7%), including pituitary adenoma (43.0%), craniopharyngioma (10.6%), and other pituitary/hypothalamic tumors (6.1%). Most patients (67.8%) had ≥ 2 additional pituitary deficiencies other than GHD (Table 1). Common comorbidities besides pituitary hormone deficiencies in ≥ 5% of patients included hypertension (15.4%), diabetes mellitus (6.0%), and arthrosis (5.1%) (Table 1). Concomitant medications prior to and post KIMS entry for replacement of other pituitary hormone deficits included levothyroxine (71.8%), glucocorticoids (59.3%), sex steroids (59.6%), and vasopressin (19.6%).

The average duration of follow-up in KIMS was 5.3 years, with a maximum duration of 18.3 years. Most patients (81%) were followed for ≤ 10 years, 16% for 10 to 15 years, and 3% for >15 years (Fig. 2A). At baseline, the mean (± SD) prescribed dose of GH was similar in males and females (0.30 ± 0.32 mg/day and 0.30 ± 0.29 mg/day, respectively); it increased to 0.39 ± 0.28 mg/day and 0.44 ± 0.30 mg/day, respectively, at year 1, and remained higher in females compared with males throughout the rest of the study (Fig. 2B).

Safety

Adverse events

A total of 8093 (51.2%) patients reported AEs during follow-up, and treatment-related AEs were reported in 2979 (18.8%) patients (Table 2). Arthralgia (4.6% for any AE and 2.6% for treatment-related AEs) and peripheral edema (3.8% for any AE and 3.1% for treatment-related AEs) were the 2 most frequently reported AEs. Median (10^{th}, 90^{th} percentile) time to onset was 1.1 (0.1, 6.6) year for any arthralgia and 0.5 (0.0, 5.4) year for any peripheral edema. Other fluid retention AEs that could potentially be induced by GH included extremity pain, myalgia, carpal tunnel syndrome, musculoskeletal pain, and paresthesia (1.1%-1.5% for any AE and 0.4%-0.8% for treatment-related AEs; Table 2). Frequencies of arthralgia, myalgia, and peripheral edema were lower with higher mean daily GH doses used in KIMS (> 0.30 mg) (Supplementary Table 1 (31)). Other AEs of interest were pituitary tumor recurrence (2.7% for any AE and 1.3% for treatment-related AEs) and type 2 diabetes mellitus (1.0% for any AE and 0.4% for treatment-related AEs; Table 2).

All-causality SAEs were experienced in 3998 (25.3%) patients, while treatment-related SAEs were reported in 680 (4.3%) (Table 2). The most frequently reported SAE was pituitary tumor recurrence (2.0% for any SAE and 1.0% for treatment-related SAEs). In addition, craniopharyngioma (mostly recurrent or worsening) SAE was reported in 0.5% of patients, myocardial infarction in 0.5%, and cerebrovascular accident in 0.8%. SAEs for infection were reported in 739 (4.7%) patients, among them 114 (0.7%) had gastroenteritis, 148 (0.9%) had pneumonia, and 32 (0.2%) had sepsis.

Impact of demographic variables on AE

Stratification by demographic variables showed potential impacts on the AE incidence rates by baseline age, GHD etiology, GHD onset, prior pituitary radiation, mean IGF-1 SDS, and mean daily GH dose prescribed in KIMS, but not by gender (Table 3). The overall observed crude rates of all-causality and treatment-related AEs were significantly higher in older patients (≥45 years), in patients with pituitary/hypothalamic tumor compared with those with idiopathic/congenital, and in patients with AO- compared with CO-GHD (Table 3). Significantly higher rates of all-causality SAEs were observed in patients with AO-GHD or without prior pituitary radiation at KIMS start, while none of the variables were significantly associated with treatment-related SAEs (Table 3). Lower IGF-1 SDS values (≤0) were statistically associated with lower rates of all-causality AEs and SAEs, but the opposite was observed for treatment-related AEs and SAEs (Table 3).

Lower rates for all types of AEs and any SAEs were observed in patients receiving mean doses of > 0.30 mg/day in KIMS compared with those on mean doses of ≤ 0.30 mg/day (Table 3). However, the significance for the correlation disappeared when the analysis for AEs was adjusted for age, gender, etiology, and follow-up time in KIMS (Supplementary Table 2 (31)).

Discontinuation

A total of 6118 patients discontinued the study (deaths excluded), with the most frequently reported causes being "patient choice" (n = 2270) and "doctor choice" (n = 1696), followed by "no reason given" (n = 1441), "country no longer active in KIMS" (n = 472), "site no longer active" (n = 205), and "patient withdrawal of informed consent" (n = 34). Study discontinuation occurred at similar rates in males and females, but more frequent in patients who were aged ≥ 45 years at KIMS start versus younger patients, and in patients with idiopathic/congenital GHD versus those with pituitary/hypothalamic tumor or other causes of GHD (Table 4).

AEs led to drug discontinuations in 1934 (12.2%) patients and dose reductions in 869 (5.5%) patients (Table 2). Of the 387 (2.5%) patients who discontinued GH treatment due to treatment-related SAEs, almost half had a neoplasm SAE (48.8% [189/387]) as the reason for drug withdrawal. The most frequently reported SAEs that led to treatment discontinuation were pituitary tumor recurrence (15.2% [59/387]), recurrence or worsening of craniopharyngioma (4.7% [18/387]), and prostate cancer (4.4% [17/387]).

Table 1. Patient characteristics at KIMS start

Number of patients, n (%)	Male (N = 7990)	Female (N = 7813)	Total[a] (N = 15,809)
Ethnicity			
Caucasian	7565 (94.7)	7353 (94.1)	14,921 (94.4)
Black	48 (0.6)	76 (1.0)	124 (0.8)
Oriental	93 (1.2)	94 (1.2)	187 (1.2)
Hispanic	26 (0.3)	49 (0.6)	75 (0.5)
African American	25 (0.3)	27 (0.3)	52 (0.3)
Asian	29 (0.4)	21 (0.3)	50 (0.3)
Other	118 (1.5)	96 (1.2)	216 (1.4)
Missing	86 (1.1)	97 (1.2)	184 (1.2)
Prior GH treatment status[b]			
Non-naïve	2382 (29.8)	2142 (27.4)	4526 (28.6)
Semi-naïve	1244 (15.6)	932 (11.9)	2176 (13.8)
True-naïve	4364 (54.6)	4739 (60.7)	9107 (57.6)
GHD onset			
Childhood-onset	2010 (25.2)	1502 (19.2)	3515 (22.2)
Adult-onset	5949 (74.5)	6290 (80.5)	12,241 (77.4)
Age, years[c]			
Mean ± SD	44.0 ± 15.9	43.8 ± 14.7	43.9 ± 15.3
Median (min, max)[d]	45.2 (5.6, 91.2)	44.4 (9.0, 88.4)	44.8 (5.6, 91.2)
Etiology of GHD			
Pituitary/hypothalamic tumor	5005 (62.6)	4430 (56.7)	9438 (59.7)
Idiopathic/congenital etiology	1714 (21.5)	1697 (21.7)	3413 (21.6)
Other etiologies	1211 (15.2)	1641 (21.0)	2853 (18.1)
Missing	60 (0.8)	45 (0.6)	105 (0.7)
Additional pituitary deficiencies[e]			
0 – 1 deficiency	2299 (28.8)	2677 (34.3)	4976 (31.5)
≥2 deficiencies	5639 (70.6)	5082 (65.1)	10,721 (67.8)
Missing	52 (0.7)	54 (0.7)	106 (0.7)
Prior pituitary radiation therapy at KIMS start[e]			
No	2964 (37.1)	2527 (32.3)	5491 (34.7)
Yes	2002 (25.1)	1934 (24.8)	3936 (24.9)
Missing or not applicable	3024 (37.9)	3352 (42.9)	6376 (40.3)
Comorbidities other than pituitary deficiencies			
Hypertension			2440 (15.4)
Diabetes			953 (6.0)
Arthrosis			811 (5.1)
Neoplasm (other than cranial tumor)			747 (4.7)
Coronary heart disease			558 (3.5)
Epilepsy			455 (2.9)
Stroke			276 (1.7)
Claudication			95 (0.6)
Daily GH dose at KIMS start			
Mean ± SD, mg	0.30 ± 0.32	0.30 ± 0.29	0.30 ± 0.30
Median (min, max)	0.20 (0.00, 5.30)	0.20 (0.00, 3.30)	0.20 (0.00, 5.30)
Observation time in KIMS[f]			
Mean ± SD, years	5.3 ± 4.5	5.2 ± 4.5	5.3 ± 4.5
Patient-years	42,394.4	40,733.9	83,128.3

Patient-years were calculated as from KIMS entry to the day of death or last visit.
Abbreviations: GH, growth hormone; GHD, growth hormone deficiency.
[a]Data on gender was missing for 6 patients.
[b]Non-naïve: patients were on GH at enrollment; semi-naïve: patients had not been receiving GH for ≥ 6 months prior to enrollment; true-naïve: patients had never received GH therapy prior to enrollment.
[c]N = 7989 for male, 7812 for female, and 15,801 for total.
[d]Minimum values as reported on case report forms.
[e]N = 15 803 for total.
[f]N = 7989 for male, 7813 for female, and 15 802 for total.

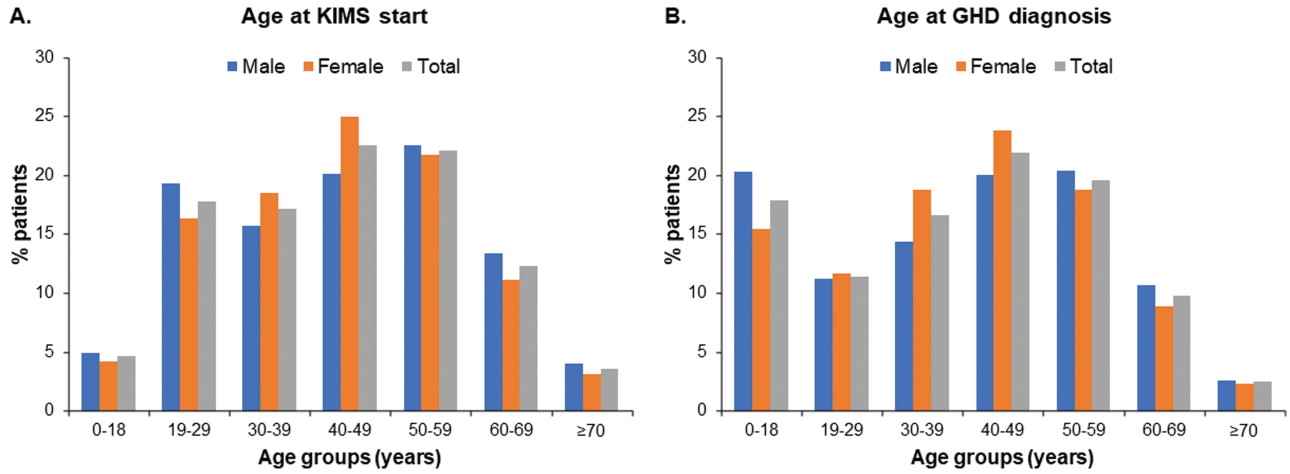

Figure 1. Age distribution of patients in the KIMS cohort at (A) KIMS start and (B) GHD diagnosis. Abbreviation: GHD, growth hormone deficiency.

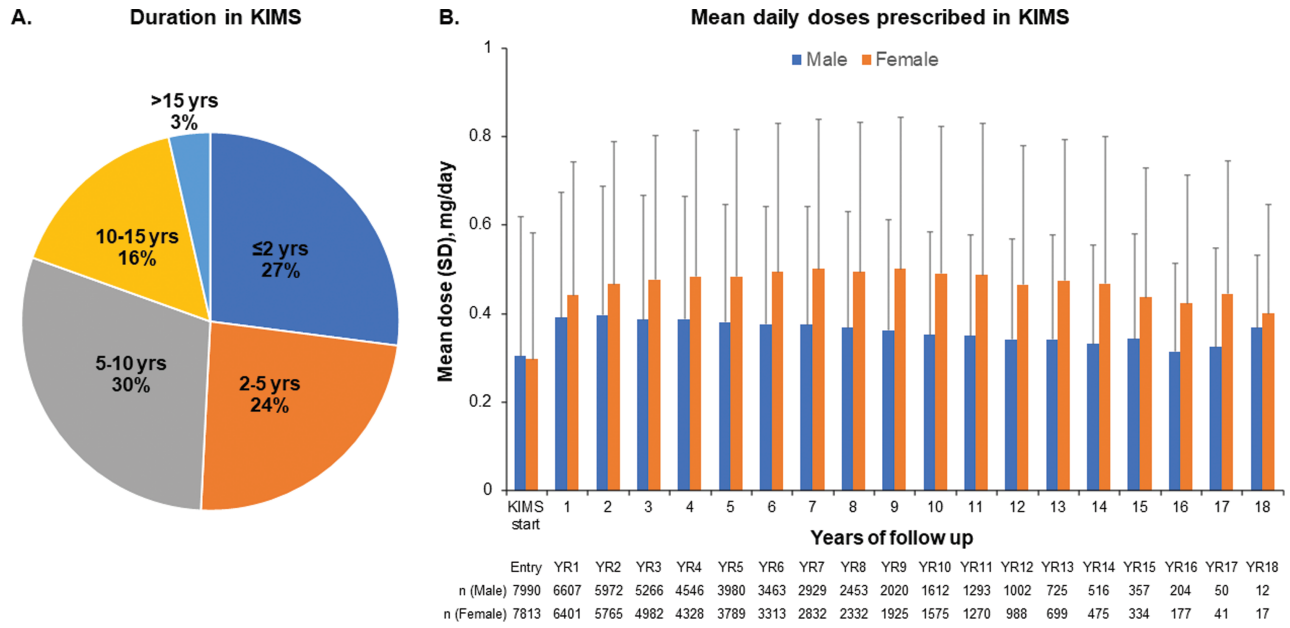

Figure 2. Duration and GH dose prescribed in KIMS. (A) A pie chart showing the distribution of patients by duration of KIMS follow-up. (B) Mean daily doses of GH prescribed over the years in KIMS. (n indicates number of patients with available data). Abbreviation: GH, growth hormone.

Mortality

Death was reported in 606 (3.8%) patients during the study. Mortality rate was numerically higher in patients who were male, aged ≥ 45 years at KIMS start, or with pituitary/hypothalamic tumor as a cause of GHD (Table 4). Causes of death were available for 560 cases, of which 65 were considered treatment-related. The most common causes were neoplasms (26.1% [146/560]), cardiac or vascular disorders (12.7% [71/560]), infections/infestations (10.7% [60/560]), and cerebrovascular disorders (8.6% [48/560]).

Cancer

In the 14 533 patients who did not have a prior history of cancer at KIMS start, 471 (3.2%) patients were diagnosed with cancer during the study. The most frequently reported (diagnosed in ≥ 20 patients) were prostate (n = 86), nonmelanoma skin (n = 57), breast (n = 39), lung (n = 37), brain (n = 29), melanoma (n = 25), and colon (n = 20) cancers. A second cancer developed in 3.2% (15/471) of patients, mostly with prostate cancer (n = 5) or nonmelanoma skin cancer (n = 4) as the first cancer. The organ affected or type of second cancers included melanoma (n = 2); follicular non-Hodgkin lymphoma (n = 1); lymphoid leukemia (n = 1); colon (n = 3); mesothelioma (n = 1); nonmelanoma skin (n = 1); prostate (n = 1); kidney (n = 1); small intestine (n = 1); heart, mediastinum and pleura (n = 1); lung (n = 1); and adrenal gland (n = 1).

The overall SIR for de novo cancer was 0.92 (95% CI, 0.83-1.01; Table 5). Compared with the general population, cancer risk was within the expected range in subgroups defined by gender, GHD onset, prior GH treatment status, prior irradiation at KIMS start, time interval in KIMS follow-up, or mean GH dose (Table 5). Stratification by calendar years showed a slightly lower SIR (0.82; 95% CI 0.69-0.98) for calendar years 2008-2012. Patients with idiopathic/congenital GHD had a lower cancer risk (0.64; 95% CI 0.43-0.91), whereas

Table 2. Commonly reported AEs (≥1% patients) and SAEs (≥0.5% patients) (N = 15 809)

Number of patients	All causality, n (%)	Treatment-related, n (%)
Patients with ≥ 1 AE	8093 (51.2)	2979 (18.8)
Patients with ≥ 1 SAE	3998 (25.3)	680 (4.3)
AEs occurring in ≥ 1% patients (by MedDRA PT)		
Arthralgia	730 (4.6)	407 (2.6)
Peripheral edema[a]	612 (3.9)	485 (3.1)
Headache	572 (3.6)	156 (1.0)
Influenza	450 (2.8)	3 (0)
Depression	447 (2.8)	35 (0.2)
Pituitary tumor recurrent	424 (2.7)	200 (1.3)
Back pain	387 (2.4)	29 (0.2)
Nasopharyngitis	330 (2.1)	3 (0)
Fatigue	322 (2.0)	78 (0.5)
Hypertension	304 (1.9)	57 (0.4)
Gastroenteritis	251 (1.6)	1 (0)
Pain in extremity	235 (1.5)	86 (0.5)
Myalgia	227 (1.4)	116 (0.7)
Diarrhea	223 (1.4)	11 (0.1)
Pneumonia	217 (1.4)	2 (0)
IGF-1 increased	193 (1.2)	158 (1.0)
Lower respiratory tract infection	189 (1.2)	0
Blood cholesterol increased	187 (1.2)	15 (0.1)
Osteoarthritis	186 (1.2)	13 (0.1)
Carpal tunnel syndrome	185 (1.2)	122 (0.8)
Dizziness	184 (1.2)	21 (0.1)
Musculoskeletal pain	176 (1.1)	62 (0.4)
Paresthesia	172 (1.1)	102 (0.6)
Chest pain	167 (1.1)	7 (0)
Type 2 diabetes mellitus	161 (1.0)	60 (0.4)
Bronchitis	158 (1.0)	2 (0)
Urinary tract infection	157 (1.0)	0
Vomiting	155 (1.0)	6 (0)
SAEs occurring in ≥ 0.5% patients (by MedDRA PT)		
Pituitary tumor recurrence	320 (2.0)	154 (1.0)
Death	143 (0.9)	21 (0.1)
Pneumonia	148 (0.9)	2 (0)
Cerebrovascular accident	122 (0.8)	5 (0)
Gastroenteritis	114 (0.7)	1 (0)
Myocardial infarction	81 (0.5)	2 (0)
Craniopharyngioma	81 (0.5)	33 (0.2)
Prostate cancer	81 (0.5)	28 (0.2)
Neoplasm recurrence	77 (0.5)	42 (0.3)
Other SAEs of interest		
Sepsis	32 (0.2)	0
Patients with drug discontinuation[b] due to AEs	1934 (12.2)	875 (5.5)
Patients with dose reduced due to AEs	869 (5.5)	699 (4.4)

Abbreviations: AE, adverse event; IGF-1, insulin-like growth factor 1; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event.
[a]Fluid retention and edema peripheral MedDRA PTs combined; patients counted once for the combined term.
[b]Discontinuation can be temporary, permanent, or delayed.

the risk in those with pituitary/hypothalamic tumor or other etiologies of GHD was not significantly different from that in the general population. SIRs were elevated in younger patients who were 15-24 years of age at baseline (2.25; 95% CI, 1.08-4.13) or attained age 25-29 (2.90; 95% CI, 1.16-5.97) or 30-34 (2.78; 95% CI, 1.39-4.97) years during follow-up, but not in most other age groups (Table 5). Mean IGF-1 SDS ≤ 0 was associated with a higher SIR (1.32; 95% CI,

Table 3. Observed crude rate (per 1000 patient-years) of AEs and SAEs by patient characteristics

	PY	All-causality AE		Related AE		All-causality SAE		Related SAE	
		Obs	Rate	Obs	Rate	Obs	Rate	Obs	Rate
Gender									
Male	42,394	12,397	292.4	1866	44.0	3354	79.1	365	8.6
Female	40,734	15,234	374.0	2385	58.6	3427	84.1	304	7.5
P			0.9250		0.1774		0.2759		0.6474
Age at KIMS start, years									
0 – 29	18,695	4382	234.4	600	32.1	991	53.0	86	4.6
30 – 44	24,477	7995	326.6	1308	53.4	1624	66.3	157	6.4
≥45	39,956	15,254	381.8	2343	58.6	4166	104.3	426	10.7
P			0.0141		0.0313		0.3052		0.0664
GHD etiology									
Idio/Cong	13,457	3413	253.6	647	48.1	639	47.5	51	3.8
Pit/Hyp	55,162	19,583	355.0	2944	53.4	5042	91.4	547	9.9
Other	14,273	4572	320.3	649	45.5	1084	75.9	71	5.0
P			<0.0001		0.0014		0.2567		0.9400
GHD onset									
CO	21,063	5433	257.9	827	39.3	1144	54.3	95	4.5
AO	61,977	22,184	357.9	3420	55.2	5631	90.9	574	9.3
P			<0.0001		0.0008		0.0345		0.3437
Prior pituitary radiation at KIMS start									
No	29,737	10,339	347.7	1640	55.2	2861	96.2	347	11.7
Yes	25,697	9280	361.1	1285	50.0	2224	86.5	197	7.7
P			<0.0001		0.0004		<0.0001		0.2971
IGF-1 SDS[a]									
≤0	26,958	8568	317.8	1546	57.3	2251	83.5	231	8.6
>0	38,515	13,520	351.0	1758	45.6	3351	87.0	310	8.0
P			<0.0001		<0.0001		<0.0001		0.0054
Daily GH dose[b]									
≤0.30 mg	29,622	10,630	358.9	1836	62.0	2938	99.2	339	11.4
>0.30 mg	53,507	17,001	317.7	2415	45.1	3843	71.8	330	6.2
P			<0.0001		<0.0001		<0.0001		0.0709

P value: at least one rate is different from the others in the comparison.
Abbreviations: AE, adverse event; AO, adult-onset; CO, childhood-onset; GH, growth hormone; GHD, growth hormone deficiency; Idio/Cong, idiopathic/congenital etiology; IGF-1, insulin-like growth factor 1; Obs, observed number of cases; Pit/Hyp, pituitary/hypothalamic tumor; PY, patient-years; SDS, standard deviation score.
[a]Based on mean IGF-1 SDS during KIMS from first to last visit.
[b]Based on mean GH doses per day during KIMS from first to last visit.

1.11-1.55), and mean IGF-1 SDS > 0 with a lower SIR (0.77; 95% CI, 0.67-0.89) (Table 5). No increased risk was found for prostate cancer (1.21; 95% CI, 0.97-1.50), colon cancer (0.66; 95% CI, 0.41-1.01), or breast cancer (0.56; 95% CI, 0.40-0.77; Table 5).

Vital Signs, IGF-1 Level, Lipid Profile, and Glucose Metabolism

Mean changes in vital signs relative to baseline were small at year 1 but continued to increase with time of follow-up for body weight, body mass index (BMI), waist circumference, and systolic BP (Table 6). No clinically significant changes were found in height, waist/hip ratio, heart rate, and diastolic BP over time (Table 6). In addition, hypertension AEs were reported in 304 (1.9%) patients, of which 57 (0.4%) were considered related to GH treatment (Table 2).

Mean (± SD) IGF-1 SDS was low at baseline (–1.3 ± 2.2) and increased to + 0.2 ± 1.7 at year 1. The improvement was sustained throughout the remaining years in KIMS, with the mean IGF-1 SDS reaching + 0.7 ± 1.5 at year 18 (Fig. 3A).

Centralized measurements showed little changes in lipids during KIMS follow-up (Fig. 3B). Three of the 387 patients (0.8%) who discontinued GH because of a treatment-related SAE stopped GH use due to increased serum cholesterol, triglycerides, or lipid concentrations.

Median fasting glucose was 4.8 mmol/L at baseline, remained at approximately 5.0 mmol/L from years 1 to 17, and was 6.3 mmol/L at year 18 based on data from 5 patients (Fig. 3C). Comparison of fasting glucose at the last observation versus baseline showed a statistically significant increase ($P < 0.0001$); however, the median change (+0.28 mmol/L) was small and not considered clinically meaningful. Among the 387 patients who discontinued GH replacement, 11

Table 4. Frequencies of study discontinuation and mortality by gender, age at KIMS start, and GHD etiology

Number of patients, n (%)	N[a]	Study discontinuation[b]	Mortality
Overall	15,809	6118 (38.7)	606 (3.8)
Gender			
Male	7990	3116 (39.0)	351 (4.4)
Female	7813	3002 (38.4)	255 (3.3)
Age at KIMS start, years			
0 – 29	3536	1328 (37.6)	67 (1.9)
30 – 44	4429	1660 (37.5)	113 (2.6)
≥45	7836	3130 (39.9)	426 (5.4)
Etiology of GHD			
Pituitary/hypothalamic tumor	9438	3533 (37.4)	444 (4.7)
Idiopathic/congenital	3413	1537 (45.0)	54 (1.6)
Other etiologies	2853	1013 (35.5)	106 (3.7)

Abbreviation: GHD, growth hormone deficiency.
[a]N was used as a denominator to calculate percentages in each row.
[b]Excluding death.

(2.8%) did so because of an impairment of glucose tolerance, 7 (1.8%) due to diabetes mellitus, 1 (0.3%) due to inadequate control of diabetes mellitus, and 3 (0.8%) due to hyperglycemia.

Discussion

The present analysis of safety outcomes for long-term GH replacement in adolescent and adult patients with GHD (n = 15 809), as prescribed in daily clinical practice in the KIMS study, confirmed a favorable safety profile of GH. AEs were experienced in 51.2% of the patients and most were not considered to be GH-related. Compared with the general population, risk of de novo cancers was not affected by gender, GHD onset, prior GH treatment status, prior pituitary radiation, nor time interval of follow-up in KIMS, but it was increased in younger patients and decreased in patients with idiopathic/congenital GHD. Finally, GH had a neutral effect on lipids and glucose metabolism.

Side effects of GH replacement are often related to fluid retention (32-34), in particular during initiation and dose titration (35-37). This is in agreement with our findings that arthralgia and peripheral edema, the 2 most common AEs in KIMS, occurred mostly within or approximately at 1 year after treatment initiation. The relatively low rates of fluid-retaining AEs (1.1%-4.6%) in KIMS compared with those reported in the US Hypopituitary Control and Complication Study (HypoCCS) (4.0%-20.0% for treatment-emergent arthralgia, peripheral edema, myalgia, paresthesia, and carpal tunnel syndrome) (33) could possibly be attributed to the low number of patients reporting increased levels of IGF-1 (Table 2), which mediates the fluid-retaining effects of GH (38), thereby suggesting that initial GH doses used in KIMS were likely lower compared with the HypoCCS cohort.

The present study showed significant differences in AE rates among subgroups by patient characteristics. Care should be taken when interpreting these results based on crude incidence rates, as the observed effects could be confounded by other factors (eg, age, etiology). Crude AE rates were found to be higher in patients who had a mean GH dose throughout KIMS of ≤ 0.30 mg/day versus > 0.30 mg/day (Table 3), but the significant correlation did not persist after adjusting for age, gender, etiology, and follow-up time (Supplementary Table 2 (31)), indicating confounder influences. In KIMS, patients more susceptible to AEs were likely prescribed lower GH doses, as is appropriate in clinical practice. However, these patients may still experience more AEs due to their underlying predisposing conditions. Furthermore, the lower rates in patients with higher mean GH doses were likely driven by longer follow-up duration (Supplementary Table 2 (31)), as side effects from GH tend to occur at early stages of treatment. As mentioned above, no correlation was observed between the AE rate and GH dose when the analysis was adjusted for age, gender, etiology, and follow-up time in KIMS. Moreover, AEs resulting from higher doses could have led to subsequent dose reduction, so that the mean GH dose, which was based on the average daily dose prescribed between the first and last visits in KIMS, may not reflect the actual dose associated with the reported AEs. A similar inverse relationship between AE rates and mean GH dose up to the first AE was also noted in a report of 2 other clinical practice studies (NordiNet IOS and ANSWER) of pediatric GH therapy (39). Therefore, our results do not support higher GH doses being safer compared with lower GH doses.

Epidemiological data suggest an association between serum IGF-1 levels and the risk of prostate, breast, and colon cancers (40), raising safety concerns of de novo neoplasia, tumor regrowth, or tumor recurrence with long-term GH replacement. While GH use is contraindicated in the presence of active malignancy (35), data from the HypoCCS study revealed no evidence for an increase in primary cancer with GH replacement in hypopituitary adults compared with the general population (41-43), and comparison of GH-treated with untreated patients showed no association between GH replacement and cancer (33, 42). In concordance with HypoCCS results, the overall risk for all-site de novo cancer among KIMS patients with GHD and no prior history of cancer is comparable to that expected in the general population (SIR 0.92; 95% CI, 0.83-1.01) after a mean follow-up of 5.3 years, and no increased risks were found for prostate (1.21; 95% CI, 0.97-1.50), colon (0.66; 95% CI, 0.41-1.01), and breast (0.56; 95% CI, 0.40-0.77) cancers. Risk for all-site cancer

Table 5. Standardized incidence ratios for cancer in patients without a prior history of cancer at KIMS start

	N	Obs	Crude incidence[a]	Exp	SIR	95% CI
Overall	14,533	418	553.7	455.5	0.92	0.83 – 1.01
Gender						
Male	7363	252	654.5	267.8	0.94	0.83 – 1.06
Female	7170	166	448.8	187.7	0.88	0.75 – 1.03
Calendar years						
Years 1993 – 1997	3353	13	400.5	13.9	0.93	0.50 – 1.60
Years 1998 – 2002	8889	98	508.3	93.7	1.05	0.85 – 1.27
Years 2003 – 2007	9586	179	570.2	192.7	0.93	0.80 – 1.08
Years 2008 – 2012	7734	128	593.4	155.2	0.82	0.69 – 0.98
GHD etiology						
Idio/Cong	3362	31	231.7	48.5	0.64	0.43 – 0.91
Pit/Hyp	9054	348	664.4	360.8	0.96	0.87 – 1.07
Other	2014	36	378.2	45.2	0.80	0.56 – 1.10
GHD onset						
CO	3096	29	165.2	23.9	1.21	0.81 – 1.74
AO	11,384	389	672.4	431.2	0.90	0.81 – 1.00
Age at KIMS start, years						
5-14	30	0	0.0	0.01	0.00	0.00 – 370.28
15-24	1974	10	99.8	4.45	2.25	1.08 – 4.13
25-34	1984	16	142.3	12.0	1.33	0.76 – 2.16
35-44	3058	56	335.1	45.8	1.22	0.92 – 1.59
45-54	3536	112	596.9	119.2	0.94	0.77 – 1.13
55-64	2704	130	970.1	166.7	0.78	0.65 – 0.93
65-74	1073	83	1731.8	95.1	0.87	0.70 – 1.08
75+	174	11	2175.9	12.2	0.90	0.45 – 1.61
Prior GH treatment status						
Non-naïve	4138	116	510.4	135.8	0.85	0.71 – 1.02
Semi-naïve	1889	26	238.5	29.4	0.88	0.58 – 1.30
True-naïve	8506	276	659.4	290.3	0.95	0.84 – 1.07
Prior radiation therapy at KIMS start						
No	5213	192	681.6	199.4	0.96	0.83 – 1.11
Yes	3344	151	687.2	143.7	1.05	0.89 – 1.23
Attained age, years						
5-9	3	0	0.0	0.0	0.00	0.00 – 0.00
10-14	17	0	0.0	0.0	0.00	0.00 – 2602.5
15-19	240	1	94.3	0.2	4.77	0.06 – 26.53
20-24	778	1	23.0	1.4	0.74	0.01 – 4.11
25-29	886	7	141.8	2.4	2.90	1.16 – 5.97
30-34	926	11	210.2	4.0	2.78	1.39 – 4.97
35-39	1130	11	173.2	7.4	1.48	0.74 – 2.66
40-44	1371	13	166.4	15.0	0.87	0.46 – 1.48
45-49	1639	25	285.8	27.3	0.92	0.59 – 1.35
50-54	1661	46	492.0	45.2	1.02	0.75 – 1.36
55-59	1775	67	715.3	69.9	0.96	0.74 – 1.22
60-64	1566	81	1065.0	85.7	0.95	0.75 – 1.17
65-69	1118	59	1087.6	85.7	0.69	0.52 – 0.89
70-74	784	55	1680.0	64.6	0.85	0.64 – 1.11
75-79	449	30	2063.4	34.4	0.87	0.59 – 1.24
80-84	143	10	2380.3	10.6	0.94	0.45 – 1.74
85+	47	1	1179.5	2.0	0.50	0.01 – 2.78
Time interval in KIMS follow-up						
Years 0-1	14,533	66	539.4	57.5	1.15	0.89 – 1.46
Years 1-3	11,222	95	485.9	100.4	0.95	0.77 – 1.16

Table 5. Continued

	N	Obs	Crude incidence[a]	Exp	SIR	95% CI
Years 3-5	8482	72	485.6	85.7	0.84	0.66 – 1.06
Years 5-10	6470	137	633.9	148.3	0.92	0.78 – 1.09
Years 10+	2553	48	661.0	63.7	0.75	0.56 – 1.00
Daily GH dose[b]						
≤0.30 mg	6835	217	807.2	219.9	0.99	0.86 – 1.13
>0.30 mg	7698	201	413.5	235.6	0.85	0.74 – 0.98
IGF-1 SDS[b]						
≤0	4235	141	582.4	107.2	1.32	1.11 – 1.55
>0	4709	204	583.0	263.3	0.77	0.67 – 0.89
Cancer type of interest						
Prostate cancer (Male)	7363	87	226.0	71.7	1.21	0.97 – 1.50
Breast cancer (Female)	7170	38	102.7	67.8	0.56	0.40 – 0.77
Colon cancer (overall)	14,533	21	27.8	31.7	0.66	0.41 – 1.01

Expected number of cases were computed based on Cancer Incidence in Five Continents Vol VIII for 1993-1997, Vol IX for 1998-2002, Vol X for 2003-2007, and Vol XI for 2008-2012 (24-27).
Abbreviations: AO, adult-onset; CO, childhood-onset; Idio/Cong, idiopathic/congenital etiology; Exp, expected number of cases; GHD, growth hormone deficiency; Obs, observed number of cases; Pit/Hyp, pituitary/hypothalamic tumor; SIR, standardized incidence ratio.
[a]Crude incidence is presented in number of cases per 100,000 patient-years.
[b]Based on mean values during KIMS from first to last visit.

Table 6. Mean changes from baseline for vital signs in KIMS

	Baseline value, Mean (SD)	Changes from baseline, mean (SD)				
		Year 1	Year 5	Year 10	Year 15	Year 18
n	14,936	10,175	6149	2587	593	10
BMI, kg/m^2	28.8 (6.9)	+0.2 (2.0)	+0.8 (2.8)	+1.4 (3.4)	+1.7 (3.7)	+2.8 (3.5)
n	15,190	10,270	6172	2589	593	10
Weight, kg	81.8 (21.5)	+0.5 (5.6)	+2.3 (8.2)	+3.7 (9.6)	+4.3 (10.8)	+7.1 (8.4)
n	15,273	10,709	6532	2742	623	11
Height, cm	168.1 (11.0)	+0.1 (1.2)	+0.1 (1.8)	-0.1 (1.9)	-0.4 (2.4)	+0.4 (1.5)
n	11,076	7065	4081	1761	403	8
WC, cm	95.8 (15.4)	-0.7 (6.3)	+1.2 (8.3)	+4.4 (18.9)	+6.2 (9.8)	+16.4 (5.3)
n	10,843	6918	4013	1712	347	7
WHR	0.9 (0.1)	-0.01 (0.07)	0.00 (0.08)	+0.02 (0.08)	+0.03 (0.08)	+0.06 (0.05)
n	14,393	9493	5708	2433	575	8
SBP, mmHg	125.7 (18.2)	-0.1 (16.4)	+1.6 (18.4)	+3.0 (19.1)	+6.3 (20.6)	+1.4 (26.4)
n	14,383	9481	5699	2430	575	8
DBP, mmHg	78.1 (10.9)	-0.3 (11.2)	-0.1 (12.1)	+0.1 (12.4)	+1.0 (12.6)	-5.0 (16.5)
n	12,778	7753	4561	1910	461	8
Heart rate	73.0 (10.5)	+0.3 (11.1)	+0.2 (11.8)	+0.5 (12.1)	-0.5 (12.4)	+4.4 (17.0)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference; WHR, waist/hip ratio.

increased in younger patients without prior cancer who had a baseline age of 15-24 years or attained age of 25-34 years, but not in other age groups, consistent with the finding of elevated cancer SIRs in patients <35 years in HypoCCS (41, 42). However, neither CO-GHD nor AO-GHD affected the risk in KIMS. Mean IGF-1 SDS during follow-up appeared to be inversely related to the risk, although further evaluations considering factors such as age, gender, etiology, and severity of GHD at KIMS start could help determine a more definitive conclusion. De novo cancer SIR was decreased in patients with idiopathic/congenital GHD in KIMS, suggesting that it is not GH treatment (which was given to the whole cohort), but rather other factors related to hypopituitarism or primary pituitary disease, that might contribute to the cancer incidence in the full cohort. In this context, it should be noted that other hormones may have tumor-promoting effects (44-48) and the risk for new neoplasms is increased in childhood-onset cancer survivors (49). Additionally, excess GH above physiological levels may be associated with increased cancer risk, as exemplified by the elevated risk of colon cancer in acromegaly patients (40, 50), and GH use in otherwise healthy adults with normal pituitary function is not supported (3, 36).

While pituitary tumor recurrence has been a concern with adult GH use, currently available data do not suggest an

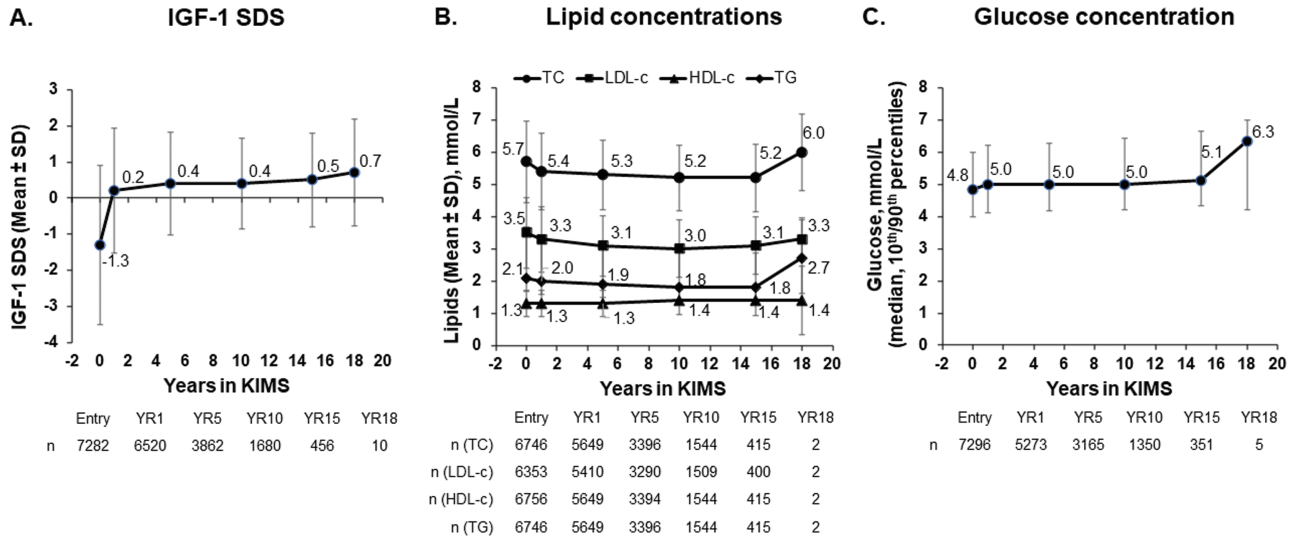

Figure 3. Evolution of (A) IGF-1 SDS, (B) centrally measured serum lipid variables and (C) concentrations of fasting blood glucose during KIMS follow-up. (n indicates number of patients with available data). Abbreviations: HDL-c, high-density-lipoprotein cholesterol; IGF-1 SDS, insulin-like growth factor-1 standard deviation score; LDL-c, low-density-lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

increased risk (17, 36). A previous case-control study reported a high frequency of pituitary tumor progression (29.1%) in a small group of patients who had surgery for a nonfunctioning pituitary adenoma and were followed in German KIMS for ≥ 5 years; however, no significant differences were found compared with the control group (51). Among all GH-treated patients in KIMS, 424 (2.7%) patients had pituitary tumor recurrence (Table 2). This rate is comparable to or lower than the rates of pituitary adenoma recurrence reported for GH-treated and untreated patients in US-HypoCCS (2.5%) (33) and global HypoCCS (7.3%) (42). These data support the fact that the pituitary tumor recurrence in KIMS is likely not associated with GH replacement.

Death was reported in 3.8% of all GH-treated patients during KIMS follow-up, most frequently due to neoplasms, cardiac or vascular disorders, infections/infestations, and cerebrovascular disorders. This is in line with the previous cause-specific mortality analysis of 13 983 patients in KIMS, which reported 528 deaths (3.8%) during a mean follow-up of 4.9 years, with the most common causes of death being malignancies, cardiovascular disease, infectious disease, and cerebrovascular disease (52). That analysis also revealed a significant negative association of mortality with IGF-1 SDS at years 1, 2, and 3, and showed that cerebrovascular mortality (irrespective of primary radiation therapy) was elevated compared with the general population, while the mortality rates due to cardiovascular diseases and malignancies were not significantly changed (52). However, as untreated controls were not included in KIMS, the relationship between GH treatment and cerebrovascular mortality cannot be connected.

GH plays an important role in lipid metabolism. Its primary effect is stimulating lipolysis in the adipose tissue, resulting in increased free fatty acid flux and decreased visceral fat (53). GH increases LDL receptor expression (54), enhances LDL catabolism (55), and increases the turnover of LDL (56) and very-low-density lipoprotein–apolipoprotein B (57). Additionally, GH replacement was shown to decrease activities of plasma lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein in GHD adults, likely contributing to the increase in high-density lipoprotein (HDL)-cholesterol concentration (58). The hypothesis that GH treatment could reverse cardiovascular risks in adult GHD patients has been addressed by numerous clinical studies. Postmarketing surveillance studies of adult GH replacement with varying follow-up durations mostly showed improvements in lipid profiles (Supplementary Table 3 (31)) (19, 20, 34, 59-63). A recent systematic review and meta-analysis found that GH treatment induced a significant reduction in LDL-cholesterol but had neutral effects on total cholesterol and HDL-cholesterol (64), which is concordant with our findings of small changes in lipids. However, the results should be evaluated with care as effects of concomitant lipid-lowering medications were not assessed in most of these studies, neither were the effects of a general tendency among clinicians to prescribe lower doses of hydrocortisone to these patients as well as higher doses of levothyroxine, the latter having a particularly marked lipid-lowering effect (65, 66).

Results concerning the effect of GH replacement on glucose metabolism have been inconsistent, with meta-analysis results showing either increased fasting glucose and insulin, or no significant changes in glucose and HbA1c (10, 64). A more recent meta-analysis of 11 randomized controlled trials and 22 prospective open-label studies found worsening glucose metabolism in adults with GHD after short-term (6-12 months) GH replacement and the elevations persisted in fasting glucose but not in other glucose hemostasis parameters with prolonged therapy (>1 year) (67). In the full KIMS cohort, the overall change in fasting glucose was small (median + 0.28 mmol/L from baseline to last observation) and median glucose concentration remained lower than diabetic levels in general, in accordance with the results from most of clinical practice studies (Supplementary Table 4 (31)) (33, 68-72). A previous KIMS analysis of 5143 patients with AO-GHD and naïve to GH treatment found a significantly higher incidence of diabetes mellitus versus the reference population, but the ratio between the observed and expected numbers of events increased with BMI and decreased with duration of GH treatment (Supplementary Table 4 (31)) (69). Notably, all the largest studies agree that the risk of developing diabetes mellitus is associated with BMI and age (18). HypoCCS also

showed comparable frequencies of impaired glucose metabolism and diabetes mellitus in GH-treated versus untreated patients (33, 72). Therefore, the occurrence of diabetes mellitus in KIMS is likely related to its classical risk factors, rather than GH replacement. Although GH antagonizes insulin action in the hepatic and peripheral tissues (53), this effect may be counterbalanced by GH decreasing visceral fat mass, thereby decreasing insulin resistance, and increasing IGF-1 levels over time, of which IGF-1 may exert its insulin-like effects (73). However, it is reasonable to be cautious when initiating GH treatment in patients older than 65 who are obese or have impaired glucose metabolism (36).

As an observational surveillance study, KIMS has inherent limitations. Data were collected during routine examinations without predefined visit windows and the reporting largely depended on investigators, which can lead to underreporting of abnormal findings. Moreover, some AEs that often present at start of GH treatment may not be captured for patients who were on GH treatment before KIMS start (28.6% non-naïve; 13.8% semi-naïve). Secondly, the analysis was limited by the incompleteness of data (eg, laboratory variables, causes of discontinuation and death) and the lack of standardization in glucose determinations (eg, fasting or nonfasting glucose in serum, plasma, or blood). Thirdly, effects of concomitant medications such as antidiabetics or lipid-lowering drugs were not assessed, and the interpretation could potentially be biased by these factors. Data interpretation may also be influenced by our analyses not considering possible inadequate replacement for other pituitary hormone deficits, which may potentially affect AE occurrence. Fourthly, although patients in KIMS were followed for an extended follow-up period of 83 128 patient-years, the mean duration of 5.3 years is still relatively short for cancer or other slow-growing tumors to be detectable, and longer follow-up may still be needed. Lastly, the majority (94.4%) of KIMS patients were Caucasian and our findings may be skewed and not readily generalizable to other ethnicities. Despite these limitations, the main strengths of this KIMS cohort included its large size, broad inclusion criteria, open-label design, and prolonged follow-up, allowing for robust data analysis and investigations of rare AEs.

Conclusion

The present KIMS analysis offers an opportunity to evaluate the safety of GH in a real-world, clinical practice setting, with the longest follow-up of > 18 years. This data from the full KIMS cohort of 15 809 patients, the largest population studied, with 83 128 patient-years of follow-up, confirms and reinforces the favorable safety profile of GH replacement in adults with GHD. No new safety signals were observed, with neutral effects on lipids or glucose metabolism. Results on de novo cancer incidence and pituitary tumor recurrence suggested no increased risks with long-term GH replacement in adults with GHD, providing further reassuring evidence that GH replacement is safe and tolerable as currently prescribed in routine clinical practice.

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Data Availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References. Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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