Pituitary
https://doi.org/10.1007/s11102-024-01459-z

Long-term metabolic effectiveness and safety of growth hormone replacement therapy in patients with adult growth hormone deficiency: a single-institution study in Japan

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Accepted: 5 September 2024

Abstract

Purpose To elucidate the long-term efficacy and safety of growth hormone replacement therapy (GHRT) in Japanese patients with adult growth hormone deficiency (AGHD).

Methods We conducted a retrospective study. A total of 110 patients with AGHD receiving GHRT were enrolled. Clinical and laboratory data were collected annually from the beginning of the study. Statistical analysis was performed using a linear mixed-effects model.

Results Of all patients, 46.4% were males, 70.9% had adult-onset GHD, and follow-up was up to 196 months, with a median of 68 months. The insulin-like growth factor-1 standard deviation score increased after the start of GHRT and remained constant for more than 11 years. Seventeen patients were followed up for more than 11 years. The body mass index increased. Waist circumference decreased in the short term but increased in the long term. The diastolic blood pressure decreased 1–5 years after the start of GHRT, and the systolic blood pressure increased 11 years after GHRT. Moreover, a long-term decrease in low-density lipoprotein cholesterol, an increase in high-density lipoprotein cholesterol, and a decrease in aspartate aminotransferase and alanine aminotransferase levels were observed. The glycosylated hemoglobin level increased after 3 years. The bone mineral density in the lumbar spine and total hip increased significantly 3 years after the start of GHRT. Finally, the number of adverse events was eight.

Conclusion We demonstrated the metabolic effectiveness and safety of GHRT in Japanese patients with AGHD over a long follow-up period of 16 years.

Keywords AGHD · GHRT · Daily GH · Metabolic effectiveness · Lipid profile · Adverse events

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Abbreviations

AGHD	Adult Growth Hormone Deficiency
GHRT	Growth Hormone Replacement Therapy
QoL	Quality of life
CO	Childhood-onset
AO	Adult-onset
BMD	Bone mineral density
SLD	Steatotic liver disease
RT	Radiotherapy
BMI	Body mass index
PG	Plasma glucose
HbA1c	Glycosylated hemoglobin
T4	Thyroxine
ITT	Insulin tolerance test

Published online: 19 September 2024

GHRP-2	GH-releasing peptide 2
AVP	Arginine vasopressin
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
IGF-I SDS	Insulin-like growth factor standard deviation score
SD	Standard deviation
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase

Introduction

Adult growth hormone deficiency (AGHD) is defined as the insufficient secretion of GH in adults. The major etiologies of AGHD include pituitary adenoma and other hypothalamic-pituitary disorders and their related therapies, such as surgery and radiotherapy, brain trauma, and congenital abnormalities [1]. AGHD is characterized by increased visceral fat, decreased lean body mass, reduced bone mineral density (BMD), abnormal lipid and glucose metabolism, metabolic dysfunction-associated steatotic liver disease (SLD), and impaired quality of life (QoL) [2–6]. Additionally, patients with AGHD exhibit an increased incidence of cardiovascular diseases, which are associated with increased mortality. Growth hormone replacement therapy (GHRT) improves these metabolic abnormalities and QoL not only in childhood-onset (CO) but also in adult-onset (AO) GHD [7–9]; however, to the best of our knowledge, few reports regarding the long-term effects of GHRT have been published [10, 11].

With regard to the risk of tumor recurrence or growth during GHRT, it has been reported that GHRT does not increase the risk of recurrence of nonfunctioning pituitary adenomas or craniopharyngiomas [12–14]. However, it is essential to continue long-term observations and accumulate data to check for the development of new malignancies or increased risk of secondary cancers.

In previous studies on the long-term efficacy and safety of GHRT in patients with AGHD, the observation period rarely exceeded 10 years and most patients were Caucasian. The impact of racial differences on the long-term efficacy of GHRT is unknown. In particular, the impact of stricter eligibility criteria for GHRT in Japan on the long-term effects of GHRT has not been examined [15]. The longest observation period for the efficacy of GHRT in a large number of Japanese patients was 8 years.

Therefore, in this study, we retrospectively examined the long-term effects and safety of GHRT in Japanese patients with AGHD at a single center for a maximum of 16 years.

Materials and methods

Study design and patients

This study was approved by the Research Ethics Committee of the Kobe University Hospital (**approval number: B230118**). The patients had the option to opt out, where they were provided with information explaining the data to be collected and the purpose of the study and were given the opportunity to withdraw.

This retrospective single-center study was conducted at Kobe University Hospital. Patients diagnosed with AGHD between April 1st, 2006 and December 31st, 2021, who had visited our department at a tertiary medical institution for at least 1 year, were retrospectively surveyed using electronic medical records. Of the 225 consecutive patients with AGHD, we enrolled 110 with no history of diabetes mellitus and who were receiving GHRT and did not meet the following exclusion criteria: lack of data before initial treatment, diagnosed with Cushing's Disease or acromegaly, lack of data on growth hormone stimulation tests in patients receiving GHRT from childhood, steroid administration other than for replacement purposes for adrenal insufficiency, GHRT interruption of more than 1 year or use of daily GH for less than 1 year, and chronic kidney disease stage 5. The patients who met these criteria were included (Fig. 1).

Safety and treatment outcomes

We investigated the clinical and laboratory data of the patients from their medical records. Available data were collected every year from the start of the study to December 31st, 2022. Clinical characteristics included sex, age, GHD onset, history of radiotherapy (RT), observation time, additional pituitary deficiencies, comorbidities, history of cerebrocardiovascular disease, and GHD etiology. Vital signs and physical findings such as blood pressure, body mass index (BMI), and abdominal circumference were measured. Laboratory data included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), plasma glucose (PG), glycosylated hemoglobin (HbA1c), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels. Patients diagnosed with hypertension, dyslipidemia, diabetes mellitus, or osteoporosis during the observation period were treated with drug therapy based on the diagnostic criteria for each disease. The presence of SLD was also investigated. SLD was defined as a diagnosis of fatty liver on abdominal ultrasonography or computed tomography. The BMD of the lumbar spine (L2–L4) and total hip were measured using dual-energy X-ray absorptiometry (DXA; Horizon A DXA System). Regarding lumbar spine bone density measurements, if the T-score differed by

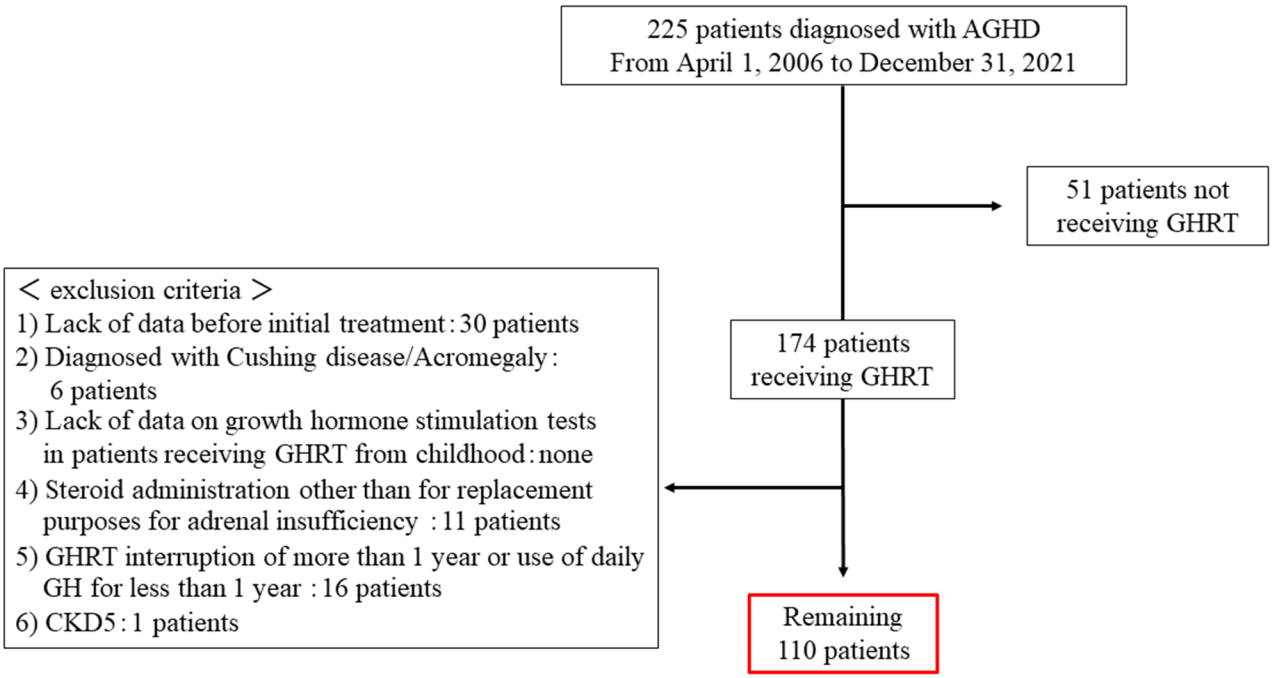

Fig. 1 Flowchart of patient selection. CKD, chronic kidney disease

more than 1.0 standard deviation (SD) compared with the adjacent vertebrae, the data were not adopted to eliminate the influence of spuriously high values due to fractures and calcifications. For safety, tumor recurrence or growth, new tumor development (including secondary tumors), and the occurrence of cerebrocardiovascular disease were investigated from medical records. Cerebrocardiovascular disease included nonfatal coronary heart disease, acute heart failure, and nonfatal cerebrovascular disease. The occurrence of these events was defined following the International Classification of Diseases, 10th Revision.

Diagnosis of AGHD, provocation tests for pituitary hormones, and hormonal assays

The diagnosis of hypopituitarism was based on the medical practice guidelines developed by the Japan Endocrine Society [16]. The insulin tolerance test (ITT) and GH-releasing peptide 2 (GHRP-2) test were performed as GH-provoked tests for the diagnosis of AGHD. For the ITT and GHRP-2 tests, severe AGHD was diagnosed if the peak serum GH concentrations were less than 1.8 ng/mL and 9.0 ng/mL, respectively [17, 18]. In Japan, GHRT is only indicated when severe AGHD is diagnosed. Provocation tests were performed using insulin (Humulin R Injection, Eli Lilly, Kobe, Japan) (0.05–0.2 unit/kg), GH-releasing peptide-2 (GHRP KAKEN 100 Injection, Kaken Pharmaceuticals, Tokyo, Japan) (100 µg), thyrotropin-releasing hormone (TRH Injection, NIPRO ES Pharma, Osaka, Japan) (200 µg), luteinizing hormone-releasing hormone (LH-RH Injection, NIPRO ES Pharma, Osaka, Japan) (100 µg), and corticotropin-releasing hormone (hCRH Injection, NIPRO ES Pharma, Osaka, Japan) (100 µg) to assess anterior pituitary function, and using the hypertonic saline solution or 1-deamino-8-D-arginine-vasopressin tests to assess posterior pituitary function. Plasma ACTH and serum levels of cortisol, GH (Tosoh, Tokyo, Japan), prolactin, LH, FSH (Abbott Japan, Tokyo, Japan), estradiol, and testosterone (LSI Medience, Tokyo, Japan) were measured using chemiluminescent enzyme immunoassays. TSH and free thyroxine (T4) levels were measured using an electrochemiluminescence immunoassay (ECLUSYS, Roche Diagnostics, Germany). Insulin-like growth factor-1 (IGF-I) levels were measured using an immunoradiometric assay kit (Daiichi Radioisotope Laboratories). IGF-I standard deviation scores (SDS) were calculated based on age- and sex-matched healthy Japanese [19]. All patients started GHRT within 1 year of the provocation tests for pituitary hormones. All patients who required thyroid and adrenal hormone replacement were started on replacement therapy between the provocation test and GHRT initiation.

Hormonal replacement in hypopituitarism

Hormonal replacement was performed according to previously reported guidelines [15, 16]. Patients with central adrenal insufficiency were administered hydrocortisone, typically at a total daily dose of 15–20 mg, either as a single

Table 1 Baseline clinical characteristics of the patients with AGHD

Characteristic	*Patients (n = 110)*
Sex, male, % (*n*)	46.4 (51)
Age, years	47.3 ± 16.6
GHD onset, AO, % (*n*)	70.9 (78)
Radiation, % (*n*)	20.0 (22)
Observation time	
Median [range], months	68 [14–196]
Additional pituitary deficiencies, % (*n*)	
ACTH	76.4 (84)
TSH	79.1 (87)
LH/FSH	56.4 (62)
AVP	28.2 (31)
Comorbidities, % (*n*)	
Hypertension	11.8 (13)
Diabetes mellitus	0.0 (0)
Dyslipidemia	32.7 (36)
SLD	60.0 (66)
History of cerebrocardiovascular events, % (*n*)	
Coronary heart disease	3.6 (4)
Cerebrovascular disease	2.7 (3)
Acute heart failure	0.9 (1)
GHD etiology, % (*n*)	
Pituitary neuroendocrine tumor	26.4 (29)
Craniopharyngioma	15.5 (17)
Rathke's cyst	15.5 (17)
Germinoma	9.1 (10)
Idiopathic/congenital etiology	9.1 (10)
Hypophysitis	4.5 (5)
Langerhans histiocytosis	0.9 (1)
Sheehan syndrome	6.4 (7)
Empty sella	3.6 (4)
Other tumors	3.6 (4)
Trauma	2.7 (3)
Other etiologies	2.7 (3)
IGF-I SDS	-3.8 ± 2.7
BMI, kg/m^2	24.2 ± 4.6
SBP, mmHg	115.1 ± 15.7
DBP, mmHg	70.6 ± 9.4
LDL-C, mg/dL	131.2 ± 36.0
HDL-C, mg/dL	52.8 ± 15.9
PG, mg/dL	83.3 ± 10.3
HbA1c, NGSP %	5.7 ± 0.3
AST, U/L	29.0 ± 13.2
ALT, U/L	29.8 ± 23.9
Zscore (lumber), SD	-0.6 ± 1.2
Zsore (total hip), SD	0.0 ± 1.2

AO, Adulthood onset; CO, Childhood onset; SLD, steatotic liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PG, plasma glucose; HbA1c, glycosylated hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase

or divided dose. For patients with central hypothyroidism, levothyroxine was administered at doses sufficient to maintain serum-free T4 levels in the mid to upper half of the reference range. Males with central hypogonadism were treated with testosterone replacement or gonadotropin therapy, whereas females with central hypogonadism received estrogen replacement or gonadotropin therapy. For patients with AGHD, GHRT was initiated with a daily GH dose of 0.2 mg for those under 60 years of age and 0.1–0.2 mg for those over 60 years of age. All patients with central hypothyroidism and central hypoadrenalism received the corresponding hormone replacement therapy. Due to lack of treatment in some because of age, only 82% of patients with hypogonadism received hormone replacement therapy.

Statistical analyses

Statistical analyses were performed using Prism version 10 (GraphPad, San Diego, CA, USA) and EZR software [20]. Differences in data were compared using the *t*-test or Mann–Whitney *U* test. The $\chi 2$ or Fisher's exact test were used to analyze categorical data. The mean of each outcome was calculated at eight time points: at the start of the observation period and 1, 2, 3, 4, 5, 6–10, and 11–16 years after the start of the observation period. Sub-analyses were performed for blood pressure, lipid profile, and BMD, excluding patients who started medications for hypertension, dyslipidemia, or osteoporosis during the observation period. A linear mixed-effects model was used to compare the values of each outcome measured before and after the observation period of GHRT at each specific time point. Fixed effects included time, whereas random effects accounted for individual patient variability. The linear mixed model implicitly assumes that data are missing at random. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics

The clinical characteristics of the patients with AGHD at the start of observation are shown in Table 1. The median age was 47.3 ± 16.6 years; 46.4% were males, and 70.9% had adult-onset GHD. The median observation period was 68 months, with the longest follow-up period being 196 months. The majority of eligible patients had multiple pituitary hormone deficiencies. No patients with diabetes mellitus, 11.8% with hypertension, 32.7% with dyslipidemia, and 60.0% with SLD were included; 6.4% had a history of

cerebrocardiovascular disease. Regarding AGHD etiology, 70% of the patients had hypothalamic-pituitary tumors.

GH dose/ IGF-I SDS

The GH dose was gradually titrated according to the IGF-I SDS normal range for age and sex, and the mean GH dose was 0.4 mg/day at 5 years after GHRT. According to the escalating GH dose, the IGF-I SDS increased substantially within the normal range (±2 SD) for more than 10 years (Fig. 2a).

Body composition

BMI gradually increased in a time-dependent manner; however, waist circumference decreased until 10 years after the start of GHRT and then increased significantly after 11 years (Fig. 2b).

Blood pressure

There was a significant decrease in diastolic blood pressure (DBP) from 1 to 5 years after the start of GHRT and a significant increase in systolic blood pressure (SBP) 11 years after GHRT (Online Resource. 1a). Moreover, a sub-analysis was performed excluding patients who started using antihypertensive medications after the start of GHRT. The results showed that SBP decreased significantly only 1 year after the start of GHRT, and DBP decreased significantly from 1 to 5 years after the start of the GHRT (Fig. 2c).

Lipid profile

Significant LDL-C reduction and HDL-C increase were observed immediately after GHRT; moreover, these changes were maintained for more than 11 years (Online Resource. 1b). Even after excluding 30 patients who started treatment for dyslipidemia after GHRT, the improvement in lipid profile was conserved (Fig. 2d).

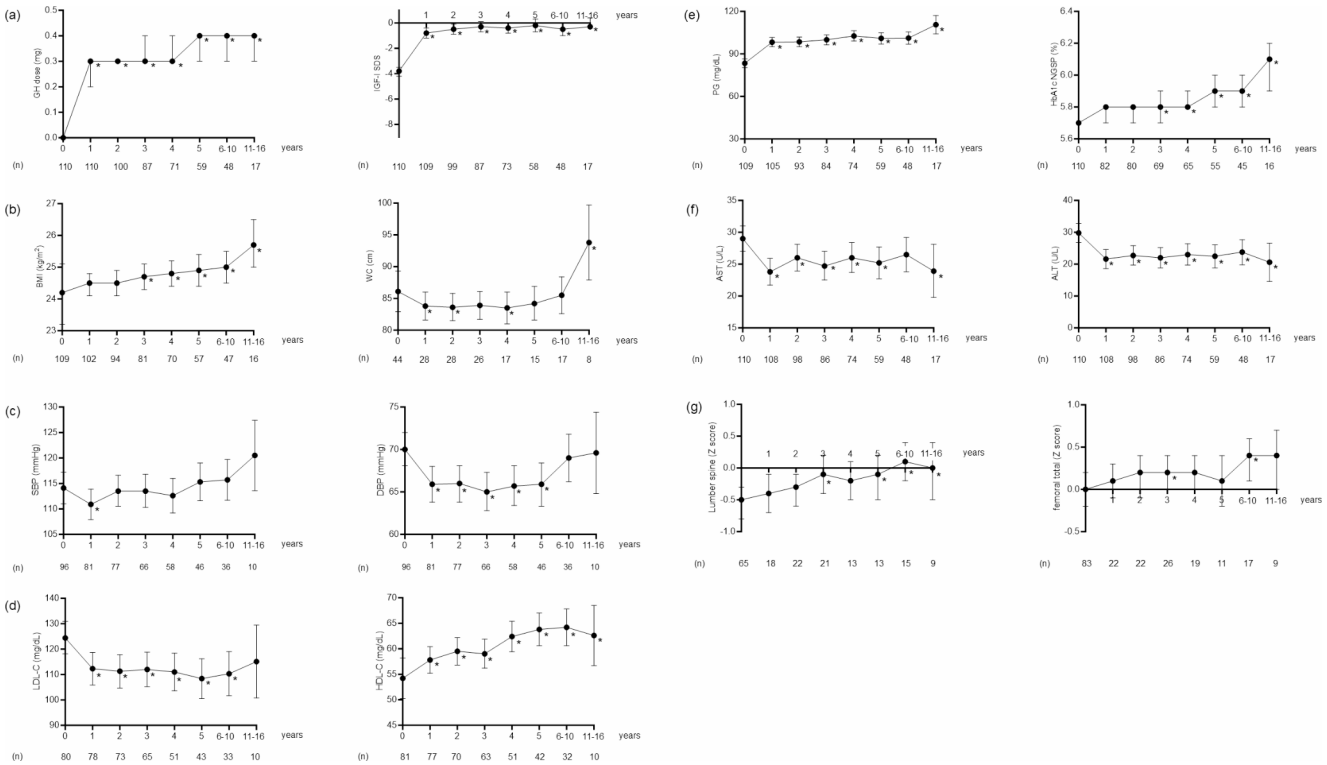

Fig. 2 Data for each outcome in patients with AGHD during the observation period. Data are presented as estimated means and error bars for 95% confidence intervals (CIs). A linear mixed-effects model was used for the analysis. A *P*-value of less than 0.05 was considered statistically significant. *: $P < 0.05$ vs. baseline. Data for GH dose/IGF-I SDS (**a**), BMI/waist circumference (**b**), SBP/DBP (**c**), LDL-C/HDL-C (**d**), PG/HbA1c (**e**), AST/ALT (**f**), and BMD of the lumbar spine and total hip (**g**). Data in (**c**), (**d**), and (**e**) exclude patients who started treatment for hypertension, dyslipidemia, and osteoporosis during the observation period. n, number of patients;. AGHD, adult growth hormone deficiency; GHRT, growth hormone replacement therapy; GH, growth hormone; IGF-I SDS, insulin-like growth factor standard deviation score; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PG, plasma glucose; BMD, bone mineral density

PG and HbA1c levels

There was a statistically significant increase in PG and HbA1c levels during the 1st and 3rd years of GHRT (Fig. 2e). Patients who started diabetes medications after starting GHRT were included, and the time of onset of diabetes mellitus varied from 2 to 12 years.

Liver function

AST and ALT levels showed a statistically significant reduction during the entire GHRT period (Fig. 2f).

BMD

BMD increased significantly 3 years after GHRT initiation in both the lumbar spine and total hip (Online Resource. 1c). Osteoporosis medication was used by 23 patients (20.9%). A significant long-term increase in BMD was maintained in the analyses that excluded users of osteoporosis medications (Fig. 2g).

Adverse events

Tumor-related, fatal and cerebrocardiovascular disease related adverse events are shown in Table 2. None of the patients had a history of RT. Adverse events included new tumor development in three patients, pituitary adenoma enlargement in two patients, secondary tumor development in one patient, and the occurrence of cerebrocardiovascular disease in two patients. The timing of adverse events was 1–12 years after GHRT initiation in all cases.

Discussion

We retrospectively analyzed the effects of GHRT for up to 16 years in a single center in the Japanese population. The sub-analysis showed the benefit of GHRT on blood pressure, lipids, and BMD, even when the effect of each treatment was excluded. In terms of death and tumor-related safety, there was no apparent increase in adverse events attributable to GHRT.

Various studies have been conducted on the long-term effects of GHRT. Similar to other studies showing an increase in BMI with long-term GHRT, especially after 10 years, BMI increased in our patients [11, 21, 22]. In contrast, waist circumference decreased but returned to baseline at 6–10 years and then increased further. In previous reports, waist circumference and body fat varied from decreased to increased [11, 21–23]. These findings suggest that the long term effects of GHRT on body composition are likely influenced by aging, lifestyle factors, and underlying pituitary diseases.

For blood pressure, a meta-analysis showed a significant reduction in DBP only; however, the studies included in this analysis all had an observation period of less than 1 year, consequently, there was a lack of long-term data [24]. As few studies have specifically excluded the effects of antihypertensive drugs and observed long-term blood pressure trends [11], the fact that a significant reduction in DBP was maintained over time without additional antihypertensive drugs is an important finding.

Regarding lipid profiles, the effects of reduced LDL-C and increased HDL-C levels have been reported to be maintained over time in prior studies; moreover some studies have reported similar trends in analyses excluding patients on lipid-lowering drugs [11, 22, 25]. The results of the present study were similar and consistently observed in different age groups, indicating the effect of GHRT.

Regarding the effect on PG and HbA1c levels, a meta-analysis reported that GHRT may increase PG levels and increase the risk of developing diabetes less than 1 year after initiation; however, long-term GHRT for more than 1 year tends to reduce the risk of developing diabetes mellitus, although fasting PG levels remain elevated [7]. Risk factors for the development of diabetes mellitus in patients with GHD include high BMI, older age, dyslipidemia, and

Table 2 List of serious adverse events in this study

No.	Sex	age	onset	cause of AGHD	RT	adverse events	years to AE onset
Neoplasm							
1	M	75	AO	Rathke's cyst	–	new onset tumor (lung cancer)	5
2	F	66	AO	Craniopharyngioma	–	new onset tumor (colon cancer)	2
3	F	23	CO	Germinoma	–	new onset tumor (glioma s/o)	5
4	M	60	AO	Pituitary adenoma	–	progressed pituitary adenoma	9
5	F	45	AO	Pituitary adenoma	–	progressed pituitary adenoma	1
6	F	67	AO	Rathke's cyst	–	secondary tumor (meningioma s/o)	3
Cerebrocardiovascular disease							
1	F	84	AO	Empty sella	–	nonfatal cerebrovascular disease	1
2	M	86	AO	Empty sella	–	acute heart failure	12

AE, adverse event; M, male; F, female; AO, adult-onset; CO, childhood-onset; RT, radiotherapy

hypertension [26]. The present study included patients with AGHD without diabetes mellitus; however, 6.3% (7 patients) developed diabetes mellitus between 2 and 12 years after GHRT initiation. Although we cannot definitively conclude that GHRT was the direct cause of diabetes onset in these seven patients, a significant increase in plasma glucose levels was consistently observed throughout the treatment period. Considering the hyperglycemic effect of GH itself, plasma glucose monitoring is necessary during GHRT.

AGHD is known to be associated with SLD (previously termed non-alcoholic steatohepatitis/non-alcoholic fatty liver disease); however, the beneficial effect of GHRT is not constant, and there are no observational studies beyond 2 years [27–29]. In studies from the UK and Brazil, GHRT reduced body fat but did not change liver fat, while a report from Japan showed a significant reduction in liver enzymes and fibrosis markers 3 months after GHRT initiation [28, 30, 31]. This difference may be due to the higher frequency of non-obese SLD among Asians and case selection bias, which may have affected treatment sensitivity to GHRT. The present study showed a sustained reduction in AST and ALT levels throughout the study period. However, a limitation of our study was that fatty liver was diagnosed only by imaging and not by liver biopsy, which is insufficient to exclude alcoholic, viral, or autoimmune hepatitis.

GHRT has been shown to significantly increase BMD in multiple long-term studies [32–34]. However, while the lumbar spine BMD continues to improve over more than 10 years, the femur exhibits sex-related differences. In males, BMD in the femur continues to increase over time, whereas in females, it peaks at 5–7 years and then gradually decreases to baseline levels [33, 34]. In the present study, both sites showed a gradual increase in BMD until the end of the observation period, which persisted even when patients receiving osteoporosis treatment were excluded, suggesting that the observed effects were attributable to the GHRT.

Meta-analyses have reported that GHRT does not increase the risk of primary cancer development or pituitary tumor recurrence [12–14, 35–37]. In a worldwide registry study that observed 15,809 patients with GHD over a maximum follow-up period of 18 years, the mortality rate was 3.8%, and the incidence of malignant tumors was 3.2%, indicating no increased risk of malignant tumors [10]. Furthermore, there was no significant increased risk of GHRT-related side effects in the elderly, with a neoplasm incidence rate of 0.15% in those aged 60 years or older and 0.77% in those younger than 60 years [23]. In a retrospective observational study in Japan, in which 334 patients received GHRT for up to 5 years, tumor-related adverse events were reported in 18 patients (5.3%). Tumor progression or recurrence was reported in 14 patients (4.2%), and new onset tumors were reported in four (1.1%), of which only one (0.29%) was malignant. However, this may be a lower estimate than other reports due to the short mean observation period of 3.1 years [38]. The present study also showed that GHRT did not increase the risk of malignant tumor development, tumor progression, or tumor recurrence.

Mortality is increased in patients with GHD and is particularly associated with cerebrocardiovascular disease [39–41]. However, data results on all-cause and cause-specific mortality rates for GH-treated adults are variable across reports, suggesting that sex may influence these findings [42]. In the present study, few cardiovascular events occurred during the observation period and were not analyzed, but the results suggest no apparent increase in cardiovascular events caused by GHRT.

This study had a few limitations. First, the sample size was small, particularly in terms of the small number of patients who could be followed up for more than 11 years. Additionally, some tests, particularly BMD, were performed in only a few patients, resulting in deficient values. Therefore, we adopted the linear mixed-effects model method of analysis, which allowed for the evaluation of participants with a variety of observation periods. Second, the blood tests performed after the start of the observation period included postprandial results. This may have influenced the PG and lipid profiles after the start of observation. Third, the medical information of the study participants was extracted solely from electronic medical records, which may have led to an underestimation of the occurrence of adverse events.

In conclusion, this study demonstrated the long-term metabolic efficacy and safety of GHRT among Japanese patients with AGHD. Among the metabolic abnormalities, improvements in the lipid profile and liver enzymes were particularly evident in the short term and sustained in the long term. The long-term safety results regarding death, new malignancies, progression, and recurrence of pituitary tumors were similar to those reported previously. Future multi-center prospective studies with a larger sample size and a comparison control group may be required to further validate our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11102-024-01459-z.

Acknowledgements The authors are grateful to the biostatisticians from the Clinical & Transrational Research Center, Kobe University Hospital, for their valuable advice concerning statistical analysis. We would like to thank Editage (www.editage.jp) for the English language editing.

Author contributions MY: Conceptualization; YOY: Data curation and Investigation; SU, HB, MK, YO, YM, YT, YS, MS, NY, MT, GI, WO, YT, and HF: Resources and Formal analysis; YOY and MY: Writing—original draft preparation and Visualization; MY, SU, YT and

HF: Writing—review and editing; MY: Project administration and Supervision. All the authors contributed to the discussion and approved the final version of the manuscript.

Funding This work was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI, grant number: 23K08008 (MY)), and the Foundation for Growth Science (MY).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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