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Investigation of the metabolic and endocrinological differences between daily and weekly growth hormone replacement therapy, somapacitan, in patients with adult growth hormone deficiency

A real-world pilot study

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Abstract

In this real-world pilot study, we evaluated the metabolic and endocrinological effects in patients with adult growth hormone deficiency (AGHD) who switched from daily growth hormone (GH) replacement therapy to weekly GH replacement therapy using somapacitan. Eleven patients with AGHD, whose medical treatment aside from GH replacement therapy did not change, were enrolled. We investigated the metabolic and endocrinological parameters between at switching and 6 months after switching from daily GH formulation to somapacitan. The results showed that body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR), fasting plasma glucose (FPG), and liver functions were significantly improved 6 months after switching compared to those at switching (each $P < .05$). Besides, the improvement in HOMA-IR was significantly associated with the period of daily GH replacement therapy before switching ($P = .048$), while age, sex, improvement in BMI or liver functions, presence of any hormonal deficiency, and the existence of any hormonal replacement therapy significantly associated ($P > .05$). In addition, switching to GH replacement therapy did not affect endocrinological parameters. In conclusion, this study might indicate that weekly GH replacement therapy with somapacitan could have more beneficial points than daily GH replacement therapy. Considering the cohort of this study was small, future studies with larger cohorts should be necessary to confirm the results of this study.

Abbreviations: ACTH = adrenocorticotropic hormone, ADH = antidiuretic hormone, AGHD = adult growth hormone deficiency, ALT = alanine aminotransferase, AST = aspartate transaminase, BMI = body mass index, FPG = fasting plasma glucose, FSH = follicle-stimulating hormone, GH = growth hormone, HbA1c = glycated hemoglobin, HOMA-IR = homeostasis model assessment of insulin resistance, HOMA-β = homeostasis model assessment of β-cell function, IGF1 = insulin-like growth factor 1, LH = luteinizing hormone, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, PRL = prolactin, γ-GTP = γ-glutamyl transferase.

Keywords: adult growth hormone deficiency, growth hormone, somapacitan

1. Introduction

Adult growth hormone deficiency (AGHD) is one of the anterior pituitary hormonal deficiencies.[1,2] Growth hormone (GH) plays important roles not only in childhood but also in adulthood. Patients with severe AGHD have fatty liver/nonalcoholic steatohepatitis (NASH)/nonalcoholic fatty liver disease (NAFLD), increased visceral adiposity, osteoporosis, poor concentration/inattention, impaired quality of

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life, coronary artery disease, and heart failure.[3–8] Moreover, Pappachan et al reported that AGHD can lead to increased mortality.[9] Hence, GH replacement therapy is essential for patients with AGHD. For a long time, daily GH replacement therapy was the only treatment available for patients with AGHD. Recently, patients with AGHD have had the opportunity to receive weekly GH replacement therapy (long-acting GH: somapacitan). The efficacy and safety of somapacitan have been revealed in some phase 3 trials,[10–12] however, no real-world study has been reported. Thus, we report the first investigation of the clinical, metabolic, and endocrinological differences between daily GH replacement therapy and weekly GH replacement therapy with somapacitan in patients with AGHD in the real world.

2. Materials and methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the ethics review committees of Fukuoka University (Fukuoka, Japan). Written informed consent was obtained from all patients for participation in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Study participants

We investigated 11 individuals with AGHD previously diagnosed with no or inadequate changes in GH levels after a GH-releasing peptide-2 test/insulin tolerance test/arginine test at Fukuoka University Chikushi Hospital and Nagasaki Prefecture Iki Hospital.[13,14] All patients had received daily GH replacement therapy for over 2 years and switched from daily GH replacement therapy to weekly GH replacement therapy with somapacitan between January 2022 and June 2022.

2.3. Methods and disease definitions

We administered and continued treatment with somapacitan for 6 months in patients with AGHD previously receiving daily GH replacement therapy. Starting doses of somapacitan were 1.5 mg/week for adults 18 to 60 years of age and 1.0 mg/week for patients aged >60 years, referring to the recommendation based on phase 3 trial in Japan (REAL Japan).[12] Dose titration was performed according to the value. Dose titration of somapacitan was performed according to the value of insulin-like growth factor 1 (IGF1) which was checked monthly after switching to somapacitan. The IGF1 value was basically checked at the morning 7 days after the injection of somapacitan (the next somapacitan injection was performed at night on the day), when the IGF1 value was assumed to be bottom in the week. If the IGF1 value was lower than −1 standard deviation score (SDS), the dose of somapacitan was increased (+0.5 mg/week). If the IGF1 value was higher than +1 standard deviation score (SDS), the dose of somapacitan was increased (−0.5 mg/week). In addition, to avoid overdose, the IGF1 value was also sometimes checked in the morning 2 to 3 days after the injection of somapacitan, when the IGF1 value was assumed to peak in the week. The following variables were examined at switching and 6 months after switching to somapacitan: parameters of glucose control (glycated hemoglobin [HbA1c], fasting plasma glucose [FPG], homeostasis model assessment of insulin resistance [HOMA-IR], and homeostasis model assessment of β-cell function [HOMA-β]), markers of lipid metabolism (low-density lipoprotein-cholesterol, high-density lipoprotein cholesterol, and triglycerides), liver functions (aspartate transaminase [AST], alanine transaminase [ALT], and gamma-glutamyl transferase [γ-GTP]), estimated glomerular filtration rate, and body mass index (BMI). Blood samples were obtained after overnight fasting, and HOMA-IR was calculated using the following formula:

HOMA-IR = FPG × fasting insulin/405

HOMA-β was calculated using the following formula:

HOMA-β = 360 × fasting insulin/(FPG − 63)

Endocrinologically, anterior pituitary hormones and related hormones (adrenocorticotropic hormone [ACTH], cortisol, TSH, free T4, luteinizing hormone [LH], follicle-stimulating hormone [FSH], and testosterone [male]/estradiol [female]) were measured at switching and 6 months after switching to somapacitan. ACTH deficiency was diagnosed by a combination of reduced ACTH and cortisol levels in the morning, and no or inadequate changes in ACTH or cortisol levels after a corticotropin-releasing hormone test. TSH deficiency was diagnosed based on a combination of reduced TSH levels, no or inadequate changes in TSH levels after a thyrotropin-releasing hormone test, and existing secondary hypothyroidism. Deficiency in LH or FSH was diagnosed by a combination of reduced LH or FSH levels, no or inadequate changes in LH or FSH levels after an LH-releasing hormone test, and existing secondary hypogonadism. Central diabetes insipidus was diagnosed by a combination of increased urinary volume; low urinary osmolarity; low antidiuretic hormone (ADH) levels compared with serum osmolarity; no or inadequate changes in ADH levels after a water restriction test/5% NaCl loading test; and increased ADH levels and decreased urinary volume after 1-desamino-8-D-arginine vasopressin administration.[13,14]

Medical treatment aside from GH replacement therapy did not change in any of the patients for the duration of this study.

2.4. Statistical analyses

Data are shown as the mean ± standard deviation (SD). Statistical analyses were performed using Stata SE version 16 (StataCorp.2019. Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC.). The Student *t* test was used to assess the significance of differences between mean values. This relationship was examined using univariate regression analysis (Fisher test). *P* value < .05 was considered significant.

3. Results

Table 1 presents the patient characteristics in our study. All patients underwent AGHD and daily GH replacement therapy. The mean age was 61.9 ± 18.9 years, and 9 patients were female. The BMI was 26.7 ± 5.2. Endocrinologically, 54.5, 54.5, 45.5, and 45.5% of the patients had ACTH, TSH, LH, and FSH deficiencies, respectively. A total of 9.1% of patients had central diabetes insipidus. In addition, hydrocortisone, levothyroxine, human chorionic gonadotrophin/human menopausal gonadotropin (HCG/HMG), and testosterone/estrogen, and desmopressin replacement therapy were performed in 54.5, 63.6, 0.0, 0.0, and 9.1% of patients (one patient did not have TSH deficiency but rather primary hypothyroidism, and was administered levothyroxine). As a result of titration, IGF1 values 6 months after switching to somapacitan were almost the same as those at switching (100.2 ± 44.3 vs 98.3 ± 40.5 ng/mL, *P* = .316). The IGF1 values of all patients at switching and 6 months after switching to somapacitan were between −1SDS and +1SDS, and the value of IGF1 at 2–3 days after the injection of somapacitan were almost the same as the 7 days after injection, which indicated larger amount of somapacitan must not be injected. The mean dose of daily GH replacement at switching was 0.20 ± 0.07 mg/day, and the dose of somapacitan 6 months after switching was 1.45 ± 0.35 mg/week (Table 2).

Table 3 shows the changes in clinical, metabolic, and endocrinological parameters.

In terms of glucose tolerance, HOMA-IR and FPG were significantly improved 6 months after switching compared with

Table 1

Characteristics of the patients in our study cohort.

	Number of patients = 11
Age (yr, ± SD)	61.9 ± 18.9
Sex (female/male)	9/2
BMI (kg/m^2, ± SD)	26.7 ± 5.2
Hormonal deficiencies	
Deficiency of ACTH (%)	54.5
Deficiency of TSH (%)	54.5
Deficiency of LH (%)	45.5
Deficiency of FSH (%)	45.5
Central diabetes insipidus (%)	9.1
Deficiency of GH (%)	100
Replacement therapies	
Hydrocortisone (%)	54.5
Levothyroxine (%)	63.6#
HCG/HMG (%)	0
Testosterone/estradiol (%)	0
Desmopressin (%)	9.1
GH (%)	100
Periods of GH replacement therapy (yr, ± SD)	6.9 ± 2.9

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, GH = growth hormone, HCG = human chorionic gonadotrophin, HMG = human menopausal gonadotropin, LH = luteinizing hormone, TSH = thyroid-stimulating hormone.
#One patient took levothyroxine for primary hypothyroidism.

Table 2

Details of GH replacement therapy in our study.

	At switching	6 mo after switching	*P*
IGF1 (ng/mL, ± SD)	100.2 ± 44.3	98.3 ± 40.5	.316
Dose of daily GH replacement before changing (mg/d)	0.20 ± 0.07	-	-
Dose of somapacitan 6 mo after changing (mg/wk)	-	1.45 ± 0.35	-

$P < .05$ was considered significant. IGF1 = insulin-like growth factor 1.

those at switching (HOMA-IR: 3.1 ± 1.6 vs 2.3 ± 1.3, $P = .022$; FPG: 104.5 ± 19.6 vs 99.3 ± 16.9 mg/dL, $P = .044$). Meanwhile, HbA1c and HOMA-β did not improve from at switching to 6 months after switching (HbA1c: 6.3 ± 0.5 vs 6.2 ± 0.5%, $P = .174$, HOMA-β: 148.0 ± 138.3 vs 110.5 ± 78.0, $P = .140$).

The markers of lipid metabolism, estimated glomerular filtration rate, and electrolyte levels did not change significantly from switching to 6 months after switching. In contrast, all measured liver functions improved significantly from at switching to 6 months after switching (AST: 23.4 ± 3.4 vs 19.8 ± 5.1 U/L, $P = .001$; ALT: 19.6 ± 5.6 vs 15.0 ± 4.4 U/L, $P = .004$; γ-GTP: 25.2 ± 16.4 vs 20.8 ± 11.1 U/L, $P = .018$, respectively).

Regarding clinical parameters, BMI improved significantly from at switching to 6 months after switching (26.7 ± 5.2 vs 26.1 ± 5.3, $P = .007$, respectively). In addition, systolic/diastolic blood pressure improved from at switching to 6 months after switching, but not significantly (142.2 ± 14.9 vs 139.4 ± 10.8/81.6 ± 10.9 vs 79.3 ± 8.4 mm Hg, $P = .253/0.182$).

Regarding endocrinological parameters, there were no differences between the values at switching and those 6 months after switching for all anterior pituitary hormones and related hormones (Table 3).

In addition, Fisher test showed that age, sex, improvement in BMI or liver functions, presence of any hormonal deficiency, and the existence of any hormonal replacement therapy were not associated with improvement in HOMA-IR. However, daily GH replacement therapy periods were significantly positively associated with improvements in HOMA-IR ($P = .048$) (Table 4).

Table 3

Changes of metabolic and endocrinological parameters between at switching and 6 mo after switching daily GH replacement therapy to weekly GH replacement therapy with somapacitan.

	At switching	6 mo after switching	*P*
BMI (kg/m^2, ± SD)	26.7 ± 5.2	26.1 ± 5.3	.007*
Systolic blood pressure (mm Hg, ± SD)	142.2 ± 14.9	139.4 ± 10.8	.253
Diastolic blood pressure (mm Hg, ± SD)	81.6 ± 10.9	79.3 ± 8.4	.182
FPG (mg/dL, ± SD)	104.5 ± 19.6	99.3 ± 16.9	.044*
HbA1c (%, ± SD)	6.3 ± 0.5	6.2 ± 0.5	.174
HOMA-IR (±SD)	3.1 ± 1.6	2.3 ± 1.3	.022*
HOMA-β (±SD)	148.0 ± 138.3	110.5 ± 78.0	.140
AST (U/L, ± SD)	23.4 ± 3.4	19.8 ± 5.1	.001*
ALT (U/L, ± SD)	19.6 ± 5.6	15.0 ± 4.4	.004*
γ-GTP (U/L, ± SD)	25.2 ± 16.4	20.8 ± 11.1	.018*
LDL-C (mg/dL, ± SD)	112.7 ± 24.0	108.6 ± 24.9	.271
HDL-C (mg/dL, ± SD)	61.0 ± 7.9	58.9 ± 10.0	.194
Triglycerides (mg/dL, ± SD)	136.6 ± 41.1	117.3 ± 30.8	.068
eGFR (mL/min/1.73m^2)	65.5 ± 34.6	63.2 ± 21.4	.081
Na (mmol/L, ± SD)	141.5 ± 2.8	141.8 ± 2.6	.341
K (mmol/L, ± SD)	3.8 ± 0.2	3.8 ± 0.5	.351
Cl (mmol/L, ± SD)	105.1 ± 2.2	105.5 ± 2.4	.276
ACTH (pg/mL, ± SD)	19.3 ± 22.0	18.2 ± 20.0	.379
Cortisol (μg/dL, ± SD)	5.7 ± 4.0	6.4 ± 5.0	.267
TSH (μIU/mL, ± SD)	2.0 ± 1.4	1.7 ± 0.7	.154
Free thyroxine (ng/dL, ± SD)	0.9 ± 0.1	1.2 ± 0.6	.063
Prolactin (ng/mL, ± SD)	15.9 ± 13.1	14.2 ± 9.3	.185
LH (mIU/mL, ± SD)	2.8 ± 1.5	3.3 ± 2.2	.114
FSH (mIU/mL, ± SD)	5.3 ± 3.5	5.4 ± 3.6	.372
Testosterone (ng/mL, ± SD) (Male only)	3.1 ± 1.3	3.4 ± 0.4	.357
Estradiol (pg/mL, ± SD) (Female only)	25.5 ± 61.0	12.5 ± 25.4	.171

γ-GTP = γ-glutamyl transferase; ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AST = aspartate transaminase; BMI = body mass index; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; GH = growth hormone; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein-cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C = low-density lipoprotein-cholesterol; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.
$P < .05$ (*) was considered significant.

4. Discussion

AGHD is one of the pituitary hormonal deficiencies (anterior pituitary hormonal deficiencies and diabetes insipidus); however, replacement therapy could not be performed before 2006 in Japan. Furthermore, daily GH replacement therapy has been the only available treatment since 2006. It is well known that GH concentrations in the blood are normally high at midnight and low in the daytime, whereas those in patients with AGHD are extremely low during the entire day. Hence, patients with AGHD commonly self-injected GH on a nightly basis (7:00 pm–8.00 pm). However, GH concentrations in the blood of patients with AGHD during the daytime would remain severely low compared to that in normal subjects because the prolonged duration of daily GH formulation was <12 hours.[15,16] Recently, patients with AGHD have been able to use somapacitan, the only weekly GH formulation in Japan. Nevertheless, the prolonged duration of somapacitan is more than 1 week, and the effect of this formulation continues throughout the day. Thus, these differences in duration could affect metabolic and endocrinological parameters.

Table 4

Relationship between improvement in HOMA-IR and metabolic parameters/endocrinological findings examined with the Fisher exact test.

	Improvement in HOMA-IR		
Regression analysis	**β (SE)**	**95% CI**	***P***
Age	−0.188 (0.378)	−1.044 to 0.668	.631
Sex	−3.290 (17.832)	−43.629 to 37.049	.858
Improvement in BMI	−2.225 (3.581)	−10.325 to 5.874	.550
Improvement in AST	0.157 (0.560)	−1.108 to 1.423	.785
Improvement in ALT	0.145 (0.303)	−0.539 to 0.829	.643
Improvement in γ-GTP	0.332 (0.508)	−0.816 to 1.480	.529
Presence of deficiency of ACTH	7.076 (13.636)	−23.772 to 37.923	.616
Presence of deficiency of TSH	7.076 (13.636)	−23.772 to 37.923	.616
Presence of deficiency of LH	0.881 (13.836)	−30.417 to 32.180	.951
Presence of deficiency of FSH	0.881 (13.836)	−30.417 to 32.180	.951
Presence of central diabetes insipidus	23.573 (22.645)	−27.653 to 74.799	.325
Replacement therapy of hydrocortisone	7.076 (13.636)	−23.772 to 37.923	.616
Replacement therapy of levothyroxine	19.222 (12.811)	−9.759 to 48.204	.168
Replacement therapy of desmopressin	23.573 (22.645)	−27.653 to 74.799	.325
Periods of daily GH replacement therapy	4.463 (1.949)	0.055 to 8.871	.048*

β = regression coefficient; γ-GTP = γ-glutamyl transferase; ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AST = aspartate transaminase; BMI = body mass index; CI = confidence interval; FSH = follicle-stimulating hormone; GH = growth hormone; HOMA-IR = homeostasis model assessment of insulin resistance; LH = luteinizing hormone; SE = standard error; TSH = thyroid-stimulating hormone.

$P < .05$ (*) was considered significant.

Patients with severe AGHD have many kinds of metabolic disorders.[3–8] AGHD must be similar to metabolic syndrome at the point of the association with obesity, insulin resistance, visceral fat, lipid profile, NASH/NAFLD, and the risk of coronary heart disease.[17–19] In our study, BMI was lower 6 months after switching to somapacitan than at switching. Since the prevalence of obesity in patients with AGHD is well known, and GH replacement therapy has been reported to improve obesity,[20] the results of our study indicate that weekly GH replacement therapy with somapacitan could be better than daily GH replacement therapy. Nevertheless, in our study, the comparison between somapacitan and the other long-acting GH formulations was not performed. Future studies could prove the existence of the difference among long-acting GH formulations. Regarding liver dysfunction, AST/ALT/γ-GTP was significantly improved by switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan. AGHD is well-known to cause NASH/NAFLD.[3,18,19] In phase 3 trials of somapacitan, the analysis of liver functions was not performed. The results of our study indicate that weekly GH replacement therapy with somapacitan could be more effective than daily GH replacement therapy, probably because continuous GH replacement therapy by somapacitan could improve liver dysfunction, considering that the values of IGF1 at switching and 6 months after switching were equivalent.

Similarly, HOMA-IR and FPG levels improved after switching from daily GH replacement therapy to somapacitan. Considering these data and the lack of change in HOMA-β, the improvement in FPG might be due to the improvement in insulin resistance. Recently, Takahashi et al reported that there were no significant differences between daily GH formulations and somapacitan, summarizing the data of phase 3 clinical trials (REAL 1 [NCT02229851], REAL 2 [NCT02382939], REAL Japan [NCT03075644]).[21] The differences could be caused that the no medical treatment of all patients in our study changed during this period, aside from GH formulations, while it is quite possible that medical treatment, aside from GH formulations, may have been changed in some patients in phase 3 trials of somapacitan.[10–12] Thus, the results of insulin tolerance in our real-world study could be different from those in the previous report by Takahashi et al.[21] Interestingly, in the same report, they also showed that the post hoc analysis of one of the phase 3 studies (REAL 1 [NCT02229851]) indicated the group receiving somapacitan had significantly lower HOMA-IR and FPG levels than those receiving daily GH formulation at 32 weeks after beginning. Moreover, the analysis also showed there were no significant differences in HbA1c values between the group receiving somapacitan and those receiving daily GH formulation. In our study, there were also no significant differences between the HbA1c values at switching and 6 months after switching to somapacitan. These results were consistent with those of the present study.

Several factors regulate insulin resistance. In our study, BMI was lower 6 months after switching to somapacitan than at the time of switching, but with a very slight difference (26.7 ± 5.2 vs $26.1 \pm 5.3\,kg/m^2$), which was difficult to explain the differences in HOMA-IR. In addition, a previous clinical trial showed no differences in body composition between the daily GH formulation and somapacitan.[10] Our study demonstrated an improvement in liver functions after switching to somapacitan, which might lead to an improvement in hepatic insulin resistance. Nonetheless, patients with AGHD may have excessive hepatic insulin resistance caused by fatty liver/NASH/NAFLD.[22] Hence, somapacitan could have more beneficial effects on insulin resistance as well as liver dysfunctions in AGHD than the daily GH formulation. On the other hand, a significant association between the improvement in HOMA-IR and liver functions was not revealed by Fisher test, probably because our study cohort was small. Thus, future studies with larger cohorts are expected to confirm the results of our study. Meanwhile, Fisher test revealed that improvement in HOMA-IR was significantly associated with the period of daily GH replacement therapy before switching to somapacitan, even though our cohort was small. These findings suggest that daily GH replacement formulation could be less efficient, at least for glucose intolerance, than somapacitan, considering that the values of IGF1 at switching and 6 months after switching were equivalent and switching from daily GH formulation to somapacitan should be considered as soon as possible if patients with AGHD were treated with daily GH replacement therapy.

We also demonstrated that switching to GH replacement therapy did not affect endocrinological parameters. Previously, it was reported that GH could have antagonistic effects against 11β-HSD1, which could lead to lower cortisol values and higher ACTH values.[23] Our study showed that ACTH and cortisol levels did not change after switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan. There were no changes in other endocrinological parameters. Hence, somapacitan can be used without impairing the endocrinological condition of patients.

Our study had some limitations. First, the sample size was small because AGHD is a rare and intractable disease; this study was a real-world pilot study; and we excluded the patients whose medical treatment, aside from GH replacement therapy, was changed during the study period. In addition, the period of our study was not so long. Hence, future studies with larger cohorts are longer observation periods are required to confirm the results of our study.

Second, we used HOMA-IR and HOMA-β as surrogate markers of insulin resistance, and insulin secretion as a substitute for an oral glucose tolerance test or hyperglycemic/

hyperinsulinemic-euglycemic clamps. In addition, our study could not reveal the mechanism of improvement of HOMA-IR and FPG adequately. Future studies are also required on this point.

Third, our study is a real-world pilot study, and thus could not check the changes in visceral fat content, bone density, bone metabolism markers, and myocardial zymogram, which were complications of AGHD. Therefore, future studies will investigate the differences between the group receiving somapacitan and those receiving daily GH formulation regarding the complications of AGHD.

5. Conclusion

Our study is the first investigation of the effects of somapacitan on metabolic and endocrinological parameters in patients with AGHD who previously received daily GH replacement therapy in a real-world pilot study and reveals that weekly GH replacement therapy with somapacitan could have more beneficial effects on liver functions than daily GH replacement therapy. Furthermore, it is possible that weekly GH replacement therapy with somapacitan could improve glucose intolerance by reducing insulin resistance compared with daily GH replacement therapy. Future studies are required to confirm and develop our study.

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References

[1] Tritos NA, Biller BMK. Current concepts of the diagnosis of adult growth hormone deficiency. Rev Endocr Metab Disord. 2021;22:109–16.
[2] Sassolas G, Chazot FB, Jaquet P, et al. GH deficiency in adults: an epidemiological approach. Eur J Endocrinol. 1999;141:595–600.
[3] Nishizawa H, Iguchi G, Murawaki A, et al. Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. Eur J Endocrinol. 2012;167:67–74.
[4] White HD, Ahmad AM, Durham BH, et al. Growth hormone replacement is important for the restoration of parathyroid hormone sensitivity and improvement in bone metabolism in older adult growth hormone-deficient patients. J Clin Endocrinol Metab. 2005;90:3371–80.
[5] Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91:1621–34.
[6] Crespo I, Santos A, Webb SM. Quality of life in patients with hypopituitarism. Curr Opin Endocrinol Diabetes Obes. 2015;22:306–12.
[7] Ishii H, Shimatsu A, Nishinaga H, et al. Assessment of quality of life on 4-year growth hormone therapy in Japanese patients with adult growth hormone deficiency: a post-marketing, multicenter, observational study. Growth Horm IGF Res. 2017;36:36–43.
[8] Ziagaki A, Blaschke D, Haverkamp W, et al. Long-term growth hormone (GH) replacement of adult GH deficiency (GHD) benefits the heart. Eur J Endocrinol. 2019;181:79–91.
[9] Pappachan JM, Raskauskiene D, Kutty VR, et al. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab. 2015;100:1405–11.
[10] Johannsson G, Gordon MB, Højby Rasmussen M, et al. Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. J Clin Endocrinol Metab. 2020;105:e1358–76.
[11] Johannsson G, Feldt-Rasmussen U, Håkonsson IH, et al. Safety and convenience of once-weekly somapacitan in adult GH deficiency. a 26-week randomized, controlled trial. Eur J Endocrinol. 2018;178:491–9.
[12] Otsuka F, Takahashi Y, Tahara S, et al. Similar safety and efficacy in previously treated adults with growth hormone deficiency randomized to once-weekly somapacitan or daily growth hormone. Clin Endocrinol (Oxf). 2020;93:620–8.
[13] Ishii K, Abe I, Kameda W, et al. Clinical investigation of pituitary incidentalomas: a two-center study. Intractable Rare Dis Res. 2019;8:239–44.
[14] Takeshita K, Abe I, Kameda W, et al. Clinical evaluations of pituitary apoplexy in incidental nonfunctional pituitary adenomas. Medicine (Baltim). 2022;101:e32026.
[15] Laursen T, Jørgensen JO, Christiansen JS. Pharmacokinetics and metabolic effects of growth hormone injected subcutaneously in growth hormone deficient patients: thigh versus abdomen. Clin Endocrinol (Oxf). 1994;40:373–8.
[16] Jørgensen JO, Flyvbjerg A, Lauritzen T, et al. Dose-response studies with biosynthetic human growth hormone (GH) in GH-deficient patients. J Clin Endocrinol Metab. 1988;67:36–40.
[17] Kohno H, Ueyama N, Honda S. Unfavourable impact of growth hormone (GH) discontinuation on body composition and cholesterol profiles after the completion of height growth in GH-deficient young adults. Diabetes Obes Metab. 1999;1:293–6.
[18] Matsumoto R, Fukuoka H, Iguchi G, et al. Long-term effects of growth hormone replacement therapy on liver function in adult patients with growth hormone deficiency. Growth Horm IGF Res. 2014;24:174–9.
[19] Burger AG, Monson JP, Colao AM, et al. Cardiovascular risk in patients with growth hormone deficiency: effects of growth hormone substitution. Endocr Pract. 2006;12:682–9.
[20] Colao A, Di Somma C, Savanelli MC, et al. Beginning to end: cardiovascular implications of growth hormone (GH) deficiency and GH therapy. Growth Horm IGF Res. 2006;16:S41–48.
[21] Takahashi Y, Biller BMK, Fukuoka H, et al. Weekly somapacitan had no adverse effects on glucose metabolism in adults with growth hormone deficiency. Pituitary. 2023;26:57–72.
[22] Takahashi Y, Iida K, Takahashi K, et al. Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency. Gastroenterology. 2007;132:938–43.
[23] Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. Endocrinology. 2001;142:1371–6.