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Metabolic Impacts of Discontinuation and Resumption of Recombinant Human Growth Hormone Treatment during the Transition Period in Patients with Childhood-Onset Growth Hormone Deficiency

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Background: Discontinuing growth hormone (GH) treatment during the transition to adulthood has been associated with adverse health outcomes in patients with childhood-onset growth hormone deficiency (CO-GHD). This study investigated the metabolic changes associated with interrupting GH treatment in adolescents with CO-GHD during the transition period.

Methods: This study included 187 patients with CO-GHD who were confirmed to have adult GHD and were treated at six academic centers in Korea. Data on clinical parameters, including anthropometric measurements, metabolic profiles, and bone mineral density (BMD) at the end of childhood GH treatment, were collected at the time of re-evaluation for GHD and 1 year after treatment resumption.

Results: Most patients (n=182, 97.3%) had organic GHD. The median age at treatment discontinuation and re-evaluation was 15.6 and 18.7 years, respectively. The median duration of treatment interruption was 2.8 years. During treatment discontinuation, body mass index Z-scores and total cholesterol, low-density lipoprotein, and non-high-density lipoprotein (HDL) cholesterol levels increased, whereas fasting glucose levels decreased. One year after GH treatment resumption, fasting glucose levels, HDL cholesterol levels, and femoral neck BMD increased significantly. Longer GH interruption (>2 years, 60.4%) resulted in worse lipid profiles at re-evaluation. The duration of interruption was positively correlated with fasting glucose and non-HDL cholesterol levels after adjusting for covariates.

Conclusion: GH treatment interruption during the transition period resulted in worse metabolic parameters, and a longer interruption period was correlated with poorer outcomes. GH treatment should be resumed early in patients with CO-GHD during the transition period.

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INTRODUCTION

Childhood-onset growth hormone deficiency (CO-GHD) is a pediatric-onset endocrine disorder that is associated with various health problems throughout life. Although the major role of growth hormone (GH) in children is to promote linear growth, it also exerts metabolic effects on multiple organs. These effects include enhancing anabolic protein metabolism, increasing bone mineral density (BMD), promoting lipolysis, and stimulating glucose metabolism [1,2]. Untreated patients with GHD have a high risk of developing cardiovascular disease [3,4], which is partially reversible with GH treatment [4,5].

CO-GHD is a heterogeneous disease that is divided into two types: idiopathic GHD, which may resolve by the time children reach their final height, and organic GHD, which usually requires continuous GH treatment during the transition period and even in adulthood [6]. Because somatic maturation continues even after the cessation of physical growth in patients with organic CO-GHD, optimal management during the transition to adulthood is crucial [2,7]. Discontinuation of GH treatment after reaching the final height has been associated with abnormal body composition, reduced BMD, an adverse metabolic profile with increased cardiovascular risk, and impaired quality of life [8-11].

Recent guidelines recommend that GH treatment should be continued until the final height is reached and resumed as early as possible after confirming adult GHD in patients with CO-GHD [12,13]. However, prolonged interruption of GH treatment between childhood and adulthood is frequently observed because of the high cost of treatment, lack of compliance, or recurrence of underlying diseases. Very few studies have explored metabolic derangements in patients with CO-GHD [14] and the adverse effects of prolonged treatment interruption in adolescents and young adults with CO-GHD in Korea [15].

We hypothesized that the interruption of GH treatment during the transition period would worsen the metabolic parameters in patients with CO-GHD, and that the duration of treatment discontinuation would be correlated with the magnitude of these changes. This multi-center study evaluated the clinical and endocrinological changes related to the discontinuation and resumption of GH treatment in patients with CO-GHD during the transition period. The effects of treatment interruption on metabolic parameters in adolescents and young adults with CO-GHD were also investigated.

METHODS

Patients

Among patients diagnosed with CO-GHD (<18 years for boys and <16 years for girls at diagnosis) between 1994 and 2019 at six academic centers in Korea, 187 patients (99 boys and 88 girls) subsequently diagnosed with adult GHD and treated with recombinant human GH for >1 year were included in this study. Patients who were not diagnosed with GHD at retest and those with adult GHD who were treated for <1 year were excluded from this study (Supplemental Fig. S1).

CO-GHD was diagnosed on the basis of a peak GH level of <10 μg/L on two separate GH stimulation tests using levodopa (125 to 500 mg) and insulin tolerance tests (regular insulin 0.1 U/kg) [13]. Patients underwent re-evaluation for GHD after they had reached their final height. Adult GHD was diagnosed on the basis of a peak GH level of <5 μg/L on insulin tolerance test [12,13]. The GH level was measured using a monoclonal immunoradiometric assay (IRMA, Diagnostics Systems Laboratories Inc., Webster, TX, USA).

GH treatment during transition

During childhood, all patients received recombinant human GH, which was discontinued when they reached their final height or when their growth velocity was <2 cm/year. GH treatment was discontinued in 27 patients before they reached their final height owing to financial constraints. Adult GHD was re-evaluated at least 1 month after GH treatment discontinuation when the patients reached their final height. After re-evaluation, patients with confirmed adult GHD received GH at a dose of 0.1 to 0.4 mg/day [12]. Patients were categorized into a long-gap group (treatment discontinuation duration >2 years) and a short-gap group (treatment discontinuation duration ≤2 years).

Clinical and biochemical assessments

Data on clinical parameters, including demographics, anthropometric measurements, and laboratory findings, were retrospectively collected at the end of childhood GH treatment, at re-

evaluation, and 1 year after treatment resumption. Height, weight, and body mass index (BMI) Z-scores were determined on the basis of the 2017 Korean National Growth Charts [16]. Overweight and obesity in children and adolescents were defined as BMIs above the 85th and 95th percentiles of the age- and sex-matched reference data, respectively [17]. In adults, overweight and obesity were defined as BMIs of >23 and >25 kg/m^2, respectively [18]. The laboratory parameters included the levels of fasting glucose, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3). Non-HDL cholesterol levels were calculated by subtracting the HDL cholesterol level from the total cholesterol level. For patients aged <19 years, dyslipidemia was defined as the presence of any of the following: total cholesterol ≥200 mg/dL, triglycerides ≥130 mg/dL, HDL cholesterol <40 mg/dL, and LDL cholesterol ≥130 mg/dL [19]; for those aged ≥19 years old, the cutoff values were as follows: total cholesterol ≥240 mg/dL, triglycerides ≥200 mg/dL, HDL cholesterol <40 mg/dL, and LDL cholesterol ≥160 mg/dL [20]. BMD was measured using dual-energy X-ray absorptiometry (DXA) scan with a Lunar Prodigy DXA system (General Electric Lunar Corporation, Madison, WI, USA) or a Hologic Discovery DXA system (Hologic Inc., Waltham, MA, USA). Z-scores for the lumbar spine and femoral neck were calculated according to the Korean reference values for children and adolescents [21,22].

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). All continuous variables were tested for normality and presented as mean±standard deviation or medians with interquartile ranges. The Student *t* test or the Mann-Whitney *U* test was used to compare continuous variables, and the chi-square test or Fisher exact test was used to compare categorical variables between the two groups. The paired *t* test, Wilcoxon signed-rank test, or McNemar test was used to compare variables among the following time points: at the end of GH treatment, at GH re-evaluation, and 1 year after treatment resumption. Linear regression analysis was performed to determine the relationship between the treatment interruption period and metabolic parameters, and multivariate models were adjusted for age, sex, BMI Z-scores, and peak GH levels at re-evaluation. After excluding patients with idiopathic GHD (n=5), statistical analyses were performed to evaluate the clinical changes of patients during GH treatment interruption and the effects of this interruption period on metabolic parameters. A P value of <0.05 was considered statistically significant.

Ethical statement

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB number: 2019-1598). The requirement of informed consent was exempted because of the retrospective nature of the study, and anonymized clinical data were used in this study.

RESULTS

Clinical characteristics of the patients

Table 1 shows the underlying etiologies of CO-GHD. Most patients (n=182, 97.3%) had organic GHD, whereas five (2.7%) had idiopathic GHD. The most common cause of GHD was craniopharyngioma (n=83, 44.4%), followed by intracranial germ cell tumor (n=49, 26.2%), and congenital hypopituitarism (n=17, 9.1%). The mean age at the time of treatment discontinuation was 15.6±2.5 years, and the mean height, weight, and BMI Z-scores were −0.92, −0.70, and −0.53, respectively (Table 2). The median duration of treatment interruption was 2.8 years

Table 1. Etiology of Childhood-Onset Growth Hormone Deficiency

Etiology	No. of patients (%)
Neoplastic	
Craniopharyngioma	83 (44.4)
Intracranial germ cell tumor	49 (26.2)
Pituitary adenoma	6 (3.2)
Optic glioma, suprasellar astrocytoma	4 (2.1)
Rathke's cleft cyst	4 (2.1)
Congenital	
Congenital hypopituitarism	17 (9.1)
Congenital structural anomaly (hydrocephalus or syringomyelia)	4 (2.1)
Infiltrative	
Hypophysitis	3 (1.6)
Langerhans cell histiocytosis	2 (1.1)
Cranial irradiation	
Cranial tumors distant from pituitary/hypothalamus area	9 (4.8)
Acute lymphoblastic leukemia	1 (0.5)
Idiopathic growth hormone deficiency	5 (2.7)

Table 2. Changes in Clinical Characteristics at the End of GH Treatment, at the Time of Re-Evaluation, and 1 Year after Treatment Resumption in Patients with Complete Data at All Visits

Characteristic	No.	At the end of GH treatment	At the time of re-evaluation	One year after GH treatment resumption	*P* (end of GH treatment vs. at re-evaluation)	*P* (at re-evaluation vs. after 1 year)
Age, yr	187	15.6±2.5	18.9±2.9	20.0±3.0	-	-
Height, cm	183	158.3±11.6	163.9±9.1	165.3±9.3	<0.001	<0.001
Weight, kg	179	56.4±14.1	65.0±15.2	67.6±15.5	<0.001	<0.001
Body mass index, kg/m^2	179	22.4±4.1	24.2±4.8	24.7±4.8	<0.001	<0.001
Height Z-score	183	−0.92±1.30	−0.70±1.48	−0.53±1.50	<0.001	<0.001
Weight Z-score	179	−0.14±1.44	0.31±1.67	0.55±1.64	<0.001	<0.001
Body mass index Z-score	179	0.40±1.42	0.77±1.66	0.93±1.66	<0.001	0.002
Overweight and/or obesity	179	59 (33.0)	86 (48.0)	103 (57.5)	<0.001	0.002
IGF-1, μg/L	150	316.3±228.9	81.1±70.0	164.0±114.7	<0.001	<0.001
IGFBP-3, μg/L	74	3,247.9±1,521.9	1,772.6±612.0	2,261.4±798.8	<0.001	< 0.001
Fasting plasma glucose, mg/dL	114	92.2±11.7	87.2±11.8	93.0±22.1	0.001	0.011
Glycated hemoglobin, %	64	5.5±0.8	5.4±0.4	5.5±1.0	0.141	0.332
Prediabetes/diabetes	57	31 (54.4)	23 (40.4)	30 (52.6)	0.096	0.118
Total cholesterol, mg/dL	130	170.6±34.1	184.7±33.6	184.3±38.9	<0.001	0.858
Triglycerides, mg/dL	66	141.8±71.2	149 9±75.4	159.6±90.0	0.412	0.510
HDL cholesterol, mg/dL	30	48.8±12.3	43.7±11.9	47.2±12.9	0.076	0.032
LDL cholesterol, mg/dL	30	103.8±30.9	121.3±40.1	113.9±34.6	0.016	0.240
Non-HDL cholesterol, mg/dL	30	131.7±26.1	144.2±38.7	139.9±38.7	0.045	0.520
Dyslipidemia	40	33 (82.5)	32 (80.0)	28 (70.0)	0.999	0.125
Lumbar spine BMD Z-score	27	-	−1.50 (−2.40 to −0.65)	−1.60 (−2.40 to −0.90)	-	0.188
Femoral neck BMD Z-score	21	-	−1.10 (−1.90 to −0.25)	−0.90 (−1.60 to −0.05)	-	0.022

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF-binding protein-3; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMD, bone mineral density.

(range, 0.1 to 16.2), and GH treatment was discontinued in 113 (60.4%) patients for >2 years. The mean age at re-evaluation for GHD was 18.9±2.9 years. The mean peak GH levels at re-evaluation were 0.30±0.54 μg/L (range, 0.01 to 4.2), and all patients except one had peak GH levels of <3 μg/L (Fig. 1). After re-evaluation, the patients received GH at a mean dose of 0.43±0.20 mg/day (0.01 mg/kg/day) for >1 year.

GH treatment-associated changes in clinical characteristics during the transition period

After the discontinuation of GH treatment, BMI Z-scores increased from 0.40 to 0.77 (P<0.001), whereas the IGF-1 and IGFBP-3 levels decreased significantly (P<0.001 for both) (Table 2). The fasting serum glucose levels decreased from 92.2 to 87.2 mg/dL (P=0.001), whereas there was not a significant change in the HbA1c levels. Total cholesterol, LDL cholesterol, and non-HDL cholesterol levels increased during the treatment interruption period (170.6 mg/dL vs. 184.7 mg/dL, P<0.001 for total cholesterol; 103.8 mg/dL vs. 121.3 mg/dL, P=0.016 for LDL cholesterol; 131.7 mg/dL vs. 144.2 mg/dL, P=0.045 for non-HDL cholesterol) (Table 2).

After 1 year of GH treatment, the IGF-1 and IGFBP-3 levels increased significantly (P<0.001 for both). Moreover, BMI Z-scores continued to increase (P=0.002). The fasting glucose levels increased from 87.2 to 93.0 mg/dL (P=0.011), and HDL cholesterol levels increased from 43.7 to 47.2 mg/dL (P=0.032) without significant changes in other components of the lipid profile. The femoral neck BMD Z-score significantly increased from −1.10 to −0.90 after GH treatment (P=0.022). Statistical analyses excluding patients with idiopathic GHD revealed results similar to those of the analyses performed including all patients (Supplemental Table S1). The changes in clinical parame-

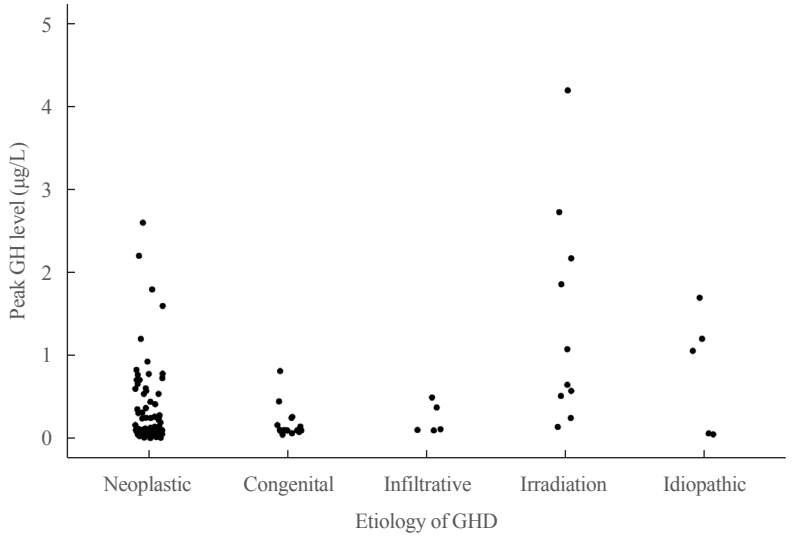

Fig. 1. Peak growth hormone (GH) levels on GH stimulation tests at re-evaluation according to the underlying etiologies of childhood-onset growth hormone deficiency (CO-GHD).

ters at two time points are described in Supplemental Tables S2 (at the end of GH treatment and at the time of GH re-evaluation) and S3 (at the time of GH re-evaluation and 1 year after treatment resumption), which showed similar results as well.

Effects of the treatment discontinuation duration on clinical characteristics

When patients were compared on the basis of the duration of treatment interruption, no significant differences were noted in metabolic parameters between the long-gap (n=113) and the short-gap (n=74) groups at the end of GH treatment (Table 3). However, at re-evaluation, the long-gap group had worse lipid profiles with higher levels of total cholesterol (186.7 mg/dL vs. 175.7 mg/dL, P=0.030), triglycerides (163.9 mg/dL vs. 125.5 mg/dL, P=0.023), LDL cholesterol (120.6 mg/dL vs. 108.0 mg/dL, P=0.029), and non-HDL cholesterol (145.8 mg/dL vs. 127.1 mg/dL, P=0.002), and lower levels of HDL cholesterol (40.3 mg/dL vs. 47.1 mg/dL, P=0.004) (Table 3). After 1 year of GH treatment, the long-gap group still had higher BMI Z-scores than the short-gap group (P=0.046). Clinical characteristics before and after GH treatment were compared for each group. The results showed significant worsening of metabolic parameters in the long-gap group (Supplemental Table S4).

In univariate regression analyses, a longer duration of GH treatment interruption was significantly correlated with increases in the levels of total cholesterol (β=1.95, P=0.018), LDL cholesterol (β=3.46, P=0.005), and non-HDL cholesterol (β=4.81, P<0.001). The duration of GH treatment interruption was inversely correlated with the levels of IGF-1 (β=−4.42, P=0.007), IGFBP-3 (β=−71.21, P=0.002), and HDL cholesterol (β=−1.06, P=0.036) at re-evaluation (Table 4). After adjusting for sex, age, BMI Z-scores, and peak GH levels, the interruption period was significantly correlated with increases in the level of fasting glucose (β=0.93, P=0.019) and non-HDL cholesterol (β=3.26, P=0.046) at re-evaluation. After adjusting for covariates, no significant associations were detected between the duration of treatment interruption and clinical parameters 1 year after treatment resumption (Supplemental Table S5). Statistical analyses performed including only patients with organic GHD revealed results consistent with those of analyses performed including all patients (Supplemental Tables S6, S7).

DISCUSSION

In this multi-center study, most patients had organic GHD with low peak GH levels at re-evaluation. GH treatment was interrupted for >2 years in 60.4% of the patients. Consequently, they experienced an increase in BMI Z-scores with worsening lipid profiles after a median of 2.8 years of treatment discontinuation during the transition period; these changes did not resolve completely after 1 year of GH treatment. One year after resuming GH treatment, the HDL cholesterol levels and femoral neck BMD showed significant improvements. Patients with a longer duration of GH treatment interruption showed worse fasting glucose levels and lipid profiles at re-evaluation.

In the present study, patients' BMI Z-scores increased, where-

Table 3. Comparison of Clinical Characteristics by the Length of GH Treatment Interruption

Variable	At the end of GH treatment				At the time of re-evaluation				One year after GH treatment resumption			
	Treatment interruption >2 years		Treatment interruption ≤2 years		Treatment interruption >2 years		Treatment interruption ≤2 years		Treatment interruption >2 years		Treatment interruption ≤2 years	
	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value	No.	Value
Body mass index, kg/m^2	112	22.2±3.9	73	22.4±4.6	113	24.6±4.9[a]	74	23.1±4.6[a]	110	25.2±4.7	71	23.8±4.8
Body mass index Z-score	112	0.5±1.3	73	0.2±1.6	113	0.91±1.71	74	0.44±1.58	110	1.12±1.65[a]	71	0.62±1.62[a]
IGF-1, μg/L	91	317.6±246.7	64	311.1±198.1	113	69.3±49.8[a]	74	94.6±85.5[a]	112	163.5±102.4	69	172.8±136.8
IGFBP-3, μg/L		3,294.0±1,566.4[a]	25	2,475.2±1,095.5[a]	85	1,788.4±672.9	18	2,152.5±943.5	85	2,272.5±863.3	32	2,396.0±905.9
Fasting glucose, mg/dL	85	93.0±12.4	44	90.4±11.7	109	87.8±13.2	70	87.3 ±10.4	97	94.7±27.5	52	91.9±13.4
Glycated hemoglobin, %	68	5.4±0.4	56	5.4±0.9	78	5.5±0.5	36	5.3±0.5	82	5.5±0.8	59	5.4±0.9
Total cholesterol, mg/dL	92	171.4±30.3	48	167.7±40.7	111	186.7±35.5[a]	70	175.7±29.0[a]	108	188.6±41.8	61	176.6±34.9
Triglycerides, mg/dL	63	146.9±77.9	20	125.0±66.8	101	163.9±137.0[a]	62	125.5±76.7[a]	88	165.3±93.8	40	138.4±70.8
HDL cholesterol, mg/dL	29	46.9±12.0	13	48.0±13.0	58	40.3±11.9[b]	54	47.1±12.6[b]	48	48.8±15.2	33	48.0±11.8
LDL cholesterol, mg/dL	29	102.5±27.6	13	103.8±30.9	58	120.6±35.2[a]	54	108.0±24.2[a]	48	112.5±34.8	33	110.5±26.7
Non-HDL cholesterol, mg/dL	29	133.3±25.9	13	123.8±25.8	58	145.8±33.1[b]	54	127.1±27.7[b]	48	137.7±37.4	33	131.8±24.8
Lumbar spine BMD Z-score	-	-	-	-	54	−1.4 (−2.4 to −0.8)	6	−1.7 (−2.7 to −0.2)	31	−1.6 (−2.4 to −0.7)	8	−1.7 (−2.8 to −1.6)
Femoral neck BMD Z-score	-	-	-	-	43	−1.0 (−1.8 to −0.3)	6	−1.6 (−2.1 to 0.2)	29	−0.9 (−1.2 to −0.1)	8	−0.9 (−1.7 to 0.2)

Values are expressed as mean±standard deviation or median (interquartile range).
GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF-binding protein-3; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMD, bone mineral density.
[a]$P<0.05$; [b]$P<0.01$.

Table 4. Associations of Clinical Characteristics with the Duration of GH Treatment Interruption (years) at Re-Evaluation

Outcome variable	Unadjusted, β (95% CI)	Adjusted, β (95% CI)[c]
Body mass index, kg/m^2	0.12 (−0.11 to 0.35)	−0.03 (−0.33 to 0.27)
Body mass index Z-score	0.04 (−0.04 to 0.12)	−0.01 (−0.10 to 0.08)
IGF-1, μg/L	−4.42 (−7.60 to −1.25)[b]	−2.19 (−5.95 to 1.57)
IGFBP-3, μg/L	−71.21 (−114.18 to −28.23)[b]	−52.00 (−105.16 to 1.16)
Fasting glucose, mg/dL	0.53 (−0.06 to 1.12)	0.93 (0.16 to 1.70)[a]
Glycated hemoglobin, %	0.01 (−0.02 to 0.04)	0.00 (−0.04 to 0.04)
Total cholesterol, mg/dL	1.95 (0.35 to 3.55)[a]	1.44 (-0.69 to 3.57)
Triglycerides, mg/dL	4.80 (−1.09 to 10.69)	4.13 (−3.84 to 12.09)
HDL cholesterol, mg/dL	−1.06 (−2.03 to −0.08)[a]	−0.79 (−2.10 to 0.51)
LDL cholesterol, mg/dL	3.46 (1.11 to 5.81)[b]	2.00 (−1.14 to 5.14)
Non-HDL cholesterol, mg/dL	4.81 (2.46 to 7.16)[b]	3.26 (0.10 to 6.42)[a]

GH, growth hormone; CI, confidence interval; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF-binding protein-3; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]$P<0.05$; [b]$P<0.01$; [c]Models were adjusted for age, sex, peak growth hormone levels at re-evaluation for body mass index and body mass index Z-scores; the models were adjusted for age, sex, body mass index Z-scores, and peak GH levels for other parameters.

as their IGF-1 and IGFBP-3 levels decreased during the GH treatment interruption period; however, their BMI Z-scores did not improve even after 1 year of GH replacement therapy. Several studies have reported that GH treatment discontinuation during the transition period led to an increase in BMI [23] and fat mass, in addition to a decrease in lean body mass [11,24,25]. Although the present study could not evaluate the body composition in detail, the increased BMI Z-scores in the cohort suggest that GH treatment discontinuation influences adiposity. Several trials have reported that GH replacement therapy during the transition period had a beneficial effect on body composition [8-11]; however, another study reported no changes in body composition after 2 years of treatment interruption [26]. A retrospective cohort study, similar to the present study, demonstrated a continual increase in BMI regardless of GH treatment during the transition period [27]. In the present study, the lack of improvement in BMI after resuming GH treatment might be attributed to the short treatment duration that was insufficient to overcome the effects of prolonged treatment interruption.

Worsening of the lipid profile, with increased levels of total cholesterol, LDL cholesterol, and non-HDL cholesterol during GH cessation, was noted in this study; however, improvements in the levels of HDL cholesterol were observed after 1 year of GH replacement therapy. GH induces lipolysis in adipocytes and plays an important role in the regulation of lipoprotein metabolism [1]; therefore, adult GHD may result in dyslipidemia and abdominal fat deposition. As observed in the present study, other studies have noted that patients with CO-GHD often experience unfavorable changes in their lipid profiles, with increased LDL cholesterol and triglyceride levels after discontinuing GH treatment when they reach their final height [28-30]. GH replacement therapy during the transition period has been associated with decreased levels of total and LDL cholesterol in some studies [10,15,27], but not all [8,26,31]. This might be related to different durations of follow-up or the heterogeneous nature of CO-GHD.

GH may enhance insulin sensitivity by improving body composition; however, it also stimulates glycogenolysis, gluconeogenesis, and lipolysis, thereby increasing blood glucose levels and inducing insulin resistance in the short term [32]. The patients in the present study had decreased fasting blood glucose levels after treatment discontinuation, which increased after treatment resumption. This is consistent with the findings of other studies [8,11,30]. Mild insulin resistance has been noted after short-term GH substitution in children and adults with GHD; however, the serum glucose levels remained within the normal range in most studies [5,33]. Long-term low-dose GH treatment may improve glucose metabolism in adult patients with GHD [3].

Although BMD was evaluated in only a small number of patients in the present study, a significant improvement was observed in femoral neck BMD after GH treatment resumption. Several studies have reported the positive effects of GH replacement therapy on bone mass when patients with CO-GHD

reached their final height [10,34,35]. Increased BMD was particularly apparent in the lumbar spine [10,34,35] but was also observed in the femoral neck [34,35]. However, the lack of changes in spine BMD and the lack of a control group in the present study made it difficult to confirm whether the observed improvement in femoral neck BMD was due to GH replacement therapy. Young adults with CO-GHD have been reported to show an initial temporary loss of BMD for several months after treatment resumption, followed by a subsequent increase in BMD [10,34]. This observation can be explained by a biphasic model of GH action, with an initial predominant bone resorption phase followed by increased bone formation [2]. Consequently, the net gain of bone mass usually takes >1 year, indicating the need for long-term follow-up to determine the real effects of GH treatment on BMD during the transition period. Attaining peak bone mass during the transition period is a crucial determinant of lifelong bone health [36], and further studies focusing on the long-term effects of GH treatment during the transition period are warranted.

In the present study, patients with a longer duration of GH treatment interruption had worse metabolic profiles and lower levels of IGF-1 at re-evaluation. After adjustment for covariates, the duration of treatment interruption was noted to be significantly associated with increases in the levels of fasting blood glucose and non-HDL cholesterol. This suggests that long-term discontinuation of GH treatment results in compromised body composition and, consequently, worsens glucose and lipid metabolism. Longer GH treatment interruption has also been associated with a worse lipid profile or lower BMD in previous studies [29,37]. Although one clinical trial reported that at least 2 years of GH cessation was safe in adolescents with good metabolic status [26], the optimal shortest period of treatment discontinuation before re-evaluation has not been clarified [38].

Current guidelines recommend re-evaluating patients for GHD at least 1 month after the discontinuation of pediatric GH treatment, particularly in patients with idiopathic isolated GHD. However, in patients with organic causes such as genetic or structural defects in the hypothalamic–pituitary region, re-evaluation is not required, and GH replacement therapy can be continued without interruption [12]. Although most patients in the present study had organic causes of GHD, the duration of GH treatment interruption was long (median, 2.8 years) because of the early discontinuation of GH treatment owing to the cost of treatment or lack of insurance coverage during the transition period. All patients except one showed peak GH levels of <3 μg/L in this study, which also supports the current recommendation that re-evaluation is not required in patients with organic causes of GHD [12]. The recent guidelines of the Korean Endocrine Society and Korean Society of Pediatric Endocrinology also recommend that GH replacement should be continued in patients with CO-GHD until they reach their final height and should be resumed as early as possible during the transition [13].

This study has some limitations. First, the retrospective design of the study resulted in missing data on some clinical parameters such as fasting glucose and insulin levels, lipid profiles, family history, nutritional status, physical activity, adherence to GH treatment, and quality of life. Furthermore, this study evaluated neither the proportion of patients with adult GHD among those with CO-GHD nor the influence of other anterior pituitary hormone deficiencies. However, most patients had organic lesions with multiple pituitary hormone deficiencies, and the sensitivity analysis showed results consistent with those of the analysis including all patients. Second, this study did not include any control group without GH treatment. Finally, the duration of GH treatment after re-evaluation was short, and the long-term consequences of GH replacement therapy could not be evaluated. Thus, the effect of GH treatment on metabolic profiles might have been misinterpreted. Nevertheless, this is the first multi-center study to demonstrate the current treatment status and importance of GH treatment in patients with CO-GHD during the transition period in Korea. Because most of these patients were confirmed to have organic GHD, the study focused on the effects of GH treatment interruption in a relatively homogeneous group of patients.

In conclusion, adolescents and young adults with CO-GHD exhibited worsened metabolic profiles after GH treatment interruption during the transition period, and these unfavorable changes were not fully reversible after 1 year of GH treatment. A longer duration of treatment discontinuation was associated with worse outcomes, and studies aiming at shortening this duration are warranted in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: C.H.S., J.H.C. Acquisition, analysis, or interpretation of data: Y.J.L., Y.C., H.W.Y., Y.A.L., C.H.S., H.S.C., H.S.K., J.H.K., J.E.M., C.W.K., M.B.A., B.K.S., J.H.C. Drafting the work or revising: Y.J.L., Y.C., J.H.C. Final approval of the manuscript: Y.J.L., Y.C., H.W.Y., Y.A.L., C.H.S., H.S.C., H.S.K., J.H.K., J.E.M., C.W.K., M.B.A., B.K.S., J.H.C.

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