The effectiveness of growth hormone replacement on energy expenditure and body composition in patients with adult growth hormone deficiency

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Abstract. Numerous studies have shown that growth hormone (GH) replacement in adult GH deficiency (AGHD) improves the body composition and metabolic rate; however, data about the relationship between body composition and energy expenditure in these patients is scarce. Our study aimed to investigate the changes in resting energy expenditure (REE) and body composition after GH replacement in patients with AGHD. We enrolled 15 patients diagnosed with AGHD and evaluated the effect of GH replacement administered once daily for 12 months on REE, body composition measured by bioelectrical impedance analysis, and serological markers. GH replacement therapy significantly increased the serum insulin growth factor-1 levels after 4, 8, and 12 months. The REE and REE/basal energy expenditure (REE/BEE) ratio significantly increased from 1278.0 ± 490.0 kcal/day and 0.87 ± 0.23 at baseline to 1505.5 ± 449.2 kcal/day and 1.11 ± 0.21 at 4 months, 1,918.7 ± 631.2 kcal/day and 1.29 ± 0.27 at 8 months, and 1,511.1 ± 271.2 kcal/day, 1.14 ± 0.29 at 12 months (p < 0.005, p < 0.01, p < 0.01, respectively). There was no change in the body weight, while the lean body mass increased significantly from 45.8 ± 9.5 kg at baseline to 46.9 ± 9.4 kg at 4 months and 47.5 ± 10.1 kg at 8 months (p < 0.005, p < 0.01, respectively). The fat mass also decreased at 12 months. Lipid metabolism improved after 4 and 8 months. GH replacement therapy in patients with AGHD significantly improved the REE and body composition.

Key words: Adult growth hormone deficiency, Resting energy expenditure, Resting metabolic rate, Body composition

GROWTH HORMONE DEFICIENCY (GHD) is a medical condition in which the pituitary gland cannot produce an adequate amount of the growth hormone (GH). Adult GHD (AGHD) commonly results from damage to the pituitary gland caused by a pituitary tumor, which has been treated with irradiation or surgical treatment, or traumatic brain injury. However, the major cause of the onset of GHD in childhood is idiopathic or congenital. AGHD has a wide range of symptoms and is characterized by abnormal body composition [1, 2] with low lean body mass and high fat mass, reduced strength and exercise capacity, metabolic disease with dyslipidemia, particularly high levels of low-density lipoprotein cholesterol (LDL-C) [3, 4], reduced bone mineral density [5, 6], and impaired psychological well-being [7]. Eventually, it increases the incidence of cardiovascular disease and mortality [8, 9]. Previous studies have shown that GH replacement in patients with AGHD has various positive effects on lipid metabolism, bone metabolism, body composition, and psychological aspects [1, 10, 11]. However, only a few studies have reported that GH replacement had positive effects on the metabolic condition and was safe in patients with AGHD [12]. The aim of this study was to investigate the energy expenditure (EE), body composition, and metabolic conditions before and after GH replacement in patients with AGHD.

Materials and Methods

Subjects
In this prospective study, fifteen patients with severe AGHD who were consistently followed up were enrolled...
between July 2009 and May 2017 at Kitasato University Hospital. They were diagnosed with structural hypothalamic/pituitary disease for which they had undergone surgery or had received irradiation and had other pituitary hormone deficiencies. Severe AGHD was defined as a peak GH response of less than 1.8 ng/mL in GH stimulation tests or less than 9 ng/mL in the GH-releasing peptide-2 test. The protocol was approved by the Kitasato University Medical School Ethics Committee (B14-45), and informed consent was obtained from all subjects. All study methods were performed in accordance with the relevant guidelines and regulations of Kitasato University Hospital as well as the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and complied with the Code of Ethics of the Helsinki Declaration.

**Study Design**

All patients were initiated on daily recombinant human GH at baseline. The dose of recombinant human GH was 0.1 mg/day (0.023 ± 0.044 mg/kg/week) by subcutaneous injection as an initiating dose for the first month, which was then increased according to each patient’s symptoms and insulin growth factor-1 (IGF-1) levels. We evaluated the resting energy expenditure (REE), basal energy expenditure (BEE), body composition measured by bioelectrical impedance analysis method, and serological markers, such as IGF-1, IGF-1 SD, total cholesterol (TC), triglyceride (TG), LDL-C, high-density lipoprotein cholesterol (HDLC), and Hba1c before and 4, 8, and 12 months after GH replacement therapy. The sample size calculation showed that to achieve a difference in \( \Delta \text{REE} \), a sample size of \( n = 9 \) was required to achieve 90% power with a type I error of 0.05, and we planned a sample size of 15 participants with GHD.

**Measure of energy expenditure and body composition**

REE and body composition were measured before and at 4, 8, and 12 months after the initiation of GH replacement therapy. REE was measured using a metabolic analyzer (MedGem®, Microlife Medical Home Solution, Inc., USA) after more than 4 hours of fasting. The measurement was performed with the patient in a sitting posture in a room (room temperature maintained between 22 and 26°C) after confirming the body temperature under 37°C and after having stayed in the same room for at least 20 min. BEE was calculated using the Harris-Benedict formula [13]. The Harris-Benedict formula for males and females is as follows: 

\[
\text{REE} = 66.47 + (13.75 \times W) + (5 \times H) - (6.75 \times A) \text{ for males}
\]

\[
\text{REE} = 665.1 + (9.563 \times W) + (1.85 \times H) - (4.676 \times A) \text{ for females}
\]

where \( W \) is the weight in kilograms, \( H \) is the height in centimeters, and \( A \) is the age in years. Body composition, including body weight (BW), fat mass (FM), and lean body mass (LBM), were measured by a body composition analyzer using the latest eight-electrode multi-frequency technology (body composition analyzer MC 180, Tanita, Japan). Patients stood with the ball of each foot in contact with the floor scale after urination. Once the weight was recorded, patients were instructed to grasp the handgrips and hold them down by their sides with the metabolic electrodes in contact with the palm and thumb. The arms were extended and kept away from the body according to the manufacturer’s instructions [14, 15]. The coefficient of variance of the impedance measurement was reported to be 0.4% [16].

**Statistical analysis**

Statistical analyses were conducted using GraphPad Prism 5.02 software (GraphPad Software Inc., San Diego, CA, USA) and JMP ver. 14 (SAS Institute, Cary, NC, USA). Data are presented as mean ± standard deviation (SD) unless otherwise indicated. The paired *t*-test and Wilcoxon signed-rank test were used to evaluate differences in the parametric or non-parametric data between the two groups. \( P < 0.05 \) was considered to indicate statistical significance.

**Results**

**Characteristics of the enrolled patients at baseline**

The baseline characteristics of the 15 patients with AGHD are shown in Table 1. The mean age of the subjects was 45.2 ± 15.4 years. Body mass index (BMI) was 23.2 ± 3.59 kg/m², and 4 patients (36.3 %) had a BMI above 25 kg/m². Their body compositions showed that LBM and FM were 45.8 ± 9.53 kg and 18.5 ± 6.14 kg, respectively. Mean IGF-1 and IGF-1 SD at baseline were 46.0 ± 31.1 (11.0–104.0) ng/mL and –4.28 ± 2.31 (–8.7– –0.6) SD, respectively, which were lower than their normal range. The mean BEE, REE, and REE/BEE ratio at baseline were 1,443.8 ± 256.5 kcal/day, 1,210 ± 126.7 kcal/day, and 0.87 ± 0.23, respectively, and REE was lower than BEE in all patients. Twelve patients had secondary hypothyroidism which was being treated with levothyroxine, 12 had secondary adrenal insufficiency which was being treated with hydrocortisone, 9 had a secondary gonadotropic deficiency, and 9 were on sexual steroid replacement therapy (Table 1). Ten patients met the criteria for dyslipidemia defined as LDL-C ≥140 mg/dL, TG ≥150 mg/dL, or HDL-C <40 mg/dL. None of the patients met the criteria for diabetes.
Serological markers

At 12 months, the mean GH replacement dose was 0.006 ± 0.002 (0.002–0.026) mg/kg/day, and 0.043 ± 0.041 (0.013–0.184) mg/kg/week. Mean IGF-1 significantly increased from 46.0 ± 31.1 ng/mL at baseline to 127.2 ± 87.2 ng/mL at 4 months (p = 0.0007), 118.7 ± 68.8 ng/mL at 8 months (p = 0.0001), and 109.6 ± 41.1 ng/mL at 12 months (p = 0.0007) (Fig. 1A). IGF-1 SD also significantly increased to –0.99 ± 2.27 SD at 4 months (p = 0.0007), –1.37 ± 2.56 SD at 8 months (p = 0.0011), and –1.28 ± 1.74 SD at 12 months (p = 0.0007) compared to –4.29 ± 2.31 SD at baseline (Fig. 1B). Thyroid-stimulating hormone significantly decreased from 2.59 ± 0.53 µU/mL at baseline to 2.98 ± 0.82 µU/mL at 4 months (p = 0.0203) and 2.99 ± 0.92 µU/mL at 8 months (p = 0.0215); however, it decreased to 2.68 ± 0.67 µU/mL at 12 months (p = 0.2676). There was no change in the serum level of free thyroxine. Serum TC concentration significantly decreased from 207.7 ± 45.9 mg/dL at baseline to 186.8 ± 33.3 mg/dL at 4 months (p = 0.0080) and 184.3 ± 44.1 mg/dL at 8 months (p = 0.0118); however, it increased to 193.7 ± 46.7 mg/dL at 12 months (p = 0.2457). Serum LDL-C concentration also significantly improved from 129.0 ± 44.5 mg/dL at baseline to 112.7 ± 28.3 mg/dL at 4 months (p = 0.0480) and 105.3 ± 41.3 mg/dL at 8 months (p = 0.0084), but it increased to 111.9 ± 39.0 mg/dL at 12 months (p = 0.1210). Serum TG levels significantly decreased from 242.1 ± 188.7 mg/dL at baseline to 169.8 ± 111.4 mg/dL at 8 months (p = 0.0302), but there was no significant

| Table 1 Characteristics of the enrolled patients with adult growth hormone deficiency |
|---------------------------------------------------------------|
| **N**, male/female | 15, 9/6 |
| Age (years) | 45.2 ± 15.4 (25–75) |
| Body mass index (kg/m²) | 23.2 ± 3.59 (17.6–29.6) |
| Body weight (kg) | 64.4 ± 13.9 (39.2–87.9) |
| Lean body mass (kg) | 45.9 ± 9.5 (27.2–59.4) |
| Fat mass (kg) | 18.5 ± 6.1 (8.4–29.5) |
| IGF-1 (ng/mL) | 46.0 ± 31.1 (11–104) |
| IGF-1 SD | –4.28 ± 2.31 (–8.7–0.6) |
| Total cholesterol (mg/dL) | 207.7 ± 45.9 (115–280) |
| Triglyceride (mg/dL) | 205.0 ± 48.7 (43–523) |
| HDL-C (mg/dL) | 56.1 ± 18.9 (26–83) |
| LDL-C (mg/dL) | 129.0 ± 44.5 (52–186) |
| Fasting plasma glucose level (mg/dL) | 97.0 ± 4.38 (87–152) |
| HbA1c (%) | 5.8 ± 0.6 (5.0–6.5) |
| BEE (kcal/day) | 1,443.8 ± 256.5 (1,067–1,852) |
| REE (kcal/day) | 1,210.0 ± 126.7 (520–2,600) |
| REE/BEE | 0.87 ± 0.23 (0.42–1.40) |
| Onset, childhood onset/adult onset | 7/8 |
| Underlying disease, N | Pituitary stalk/Craniopharyngioma/Pituitary adenoma/Others | 4/3/2/6 |
| Replacement, N (male/female) | Hydrocortisone | 12 (8/4) |
| | Levothyroxine | 12 (8/4) |
| | Sexual steroid | 9 (7/2) |
| | Desmopressin | 5 (5/0) |

Data are mean ± SD (range).
IGF-1, insulin-like growth factor-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, Hemoglobin A1c; BEE, basal energy expenditure; REE, resting energy expenditure.
change at 4 months and 12 months (169.8 ± 60.5 mg/dL, \( p = 0.2803 \); 153.4 ± 67.2 mg/dL, \( p = 0.0883 \), respectively). Serum HDL-C level did not change significantly throughout the study period. HbA1c did not change from 5.8 ± 0.6% at baseline to 5.9 ± 0.7% at 12 months (\( p = 0.4301 \)). There was no difference in the changes in hormone levels, lipid metabolism, and glucose metabolism between the sexes.

**Energy expenditure**

REE significantly increased from 1,278.0 ± 490.9 kcal/day at baseline to 1,505.5 ± 449.2 kcal/day at 4 months (\( p = 0.0020 \)), to 1,918.7 ± 631.2 kcal/day at 8 months (\( p = 0.0078 \)), and to 1,511.1 ± 271.1 kcal/day at 12 months (\( p = 0.0091 \)) (Fig. 2A). REE/BEE ratio also significantly improved from 0.87 ± 0.24 at baseline to 1.11 ± 0.21 at 4 months (\( p = 0.0020 \)), to 1.29 ± 0.27 at 8 months (\( p = 0.0078 \)), and to 1.15 ± 0.29 at 12 months (\( p = 0.0039 \)) (Fig. 2B). The change in the ratio of REE/BEE after GH replacement was 149.9 ± 43.2% and was higher in females than in males (175.3 ± 59.0% vs. 132.9 ± 16.8%, \( p = 0.0591 \)). Furthermore, univariate linear regression analysis showed that the change in the ratio of REE/BEE did not correlate with age, BMI, LBM, IGF-1 level, IGF-1 SD, HbA1c at baseline, GH dose at 12 months, and use of levothyroxine, hydrocortisone, or sexual steroids; however, it correlated with REE and REE/BEE at baseline (\( r = -0.58, p = 0.0239; r = -0.58, p = 0.0233 \), respectively).

REE/LBM ratio significantly increased from 27.8 ± 7.9 kcal/kg at baseline to 34.9 ± 6.5 kcal/kg at 4 months (\( p = 0.0039 \), 40.8 ± 7.4 kcal/kg at 8 months (\( p = 0.0156 \), and 36.2 ± 9.9 kcal/kg at 12 months (\( p = 0.0039 \)) (Fig. 2C). Six patients had an increase in appetite during the study period. Baseline REE was significantly correlated with BW (\( r = 0.53; p < 0.05 \)) and LBM (\( r = 0.60; p < 0.05 \); however, the change in REE after GH replacement did not correlate with the change in BW and LBM. The mean rate of change in REE from baseline was 135.1 ± 23.9%, 146.2 ± 60.3%, and 148.9 ± 35.7% at 4, 8, and 12 months, respectively.
Body composition

No significant changes in BW were seen, from 64.4 ± 13.9 kg at baseline to 64.8 ± 13.8 kg, 64.7 ± 13.9 kg, and 63.7 ± 13.5 kg at 4, 8, and 12 months, respectively (Fig. 3A). LBM increased significantly from 45.9 ± 9.5 kg at baseline to 47.0 ± 9.5 kg and 47.5 ± 10.1 kg at 4 and 8 months (p = 0.0018, p = 0.0083, respectively); however, there was a decrease to 47.3 ± 10.0 kg at 12 months (p = 0.0514) (Fig. 3B). FM did not show any decrease at 4 and 8 months; however, it decreased significantly from 18.5 ± 6.1 kg at baseline to 16.4 ± 5.6 kg at 12 months (p = 0.0038) (Fig. 3C). However, the change in LBM and FM after GH replacement did not correlate with the change in IGF-1 levels throughout the study period. The dose of GH replacement also did not correlate with the change in LBM and FM.

Safety

Six patients experienced adverse effects of GH replacement; however, most were not severe. There was mild edema in 3 patients, slight arthritis in 3 patients, and both edema and arthritis in 1 patient. In 2 patients, arthritis was resolved with a reduction in the GH dose. Additionally, the levophyroxine dosage was increased in 2 patients and reduced in 1 patient. The dose of hydrocortisone was increased in 3 patients during the study period.

Discussion

It is reported that REE is lower than the predicted data for age, height, and BW in patients with AGHD [1, 2]. Previous studies have shown that GH replacement for AGHD increases the metabolic rate [1, 10]. The efficacy and safety of GH treatment in Japanese adult patients with GHD have been previously reported [12]; however, there is no data about the effect of GH replacement on the EE of patients with AGHD. In this study, we evaluated the change in REE and body composition, including serological changes after GH replacement, and the safety of GH in patients with AGHD. We confirmed that GH replacement increased IGF-1 and improved the REE and body composition, there was especially an increase in LBM.

The first GH replacement study was reported in 1989. The effect of 6 months of GH replacement therapy in patients with AGHD was described. It was noted that IGF-1, LBM, and FM significantly improved in the GH treatment group compared with that in the placebo group [1]. In addition, it was confirmed that the basal metabolic rate per kilogram of LBM increased after GH treatment. It has been demonstrated that the brown adipose tissue is characterized by a high mitochondrial content to maintain the body temperature and is involved in energy expenditure, and GH increases the energy expenditure by binding to the adipose GH receptors [17]. This pathway is considered as one of the mechanisms that increases the REE by GH replacement therapy in patients with AGHD. In a previous study, the resting metabolic rate measured using the doubly labeled water method increased by 15% after 14 days of GH therapy [10]. Similarly, REE rapidly increased in the first 4 months of our study. REE at baseline, 4 months, and 8 months significantly correlated with BW and LBM; however, the change in REE after GH replacement did not correlate with the change in BW and LBM. There was a significant increase in serum free triiodothyronine after GH treatment, although there was no significant change in the serum level of free thyroxine. Another study demonstrated that GH replacement increases triiodothyronine by stimulating the conversion of peripheral thyroxine to triiodothyronine [18]. These changes in serum free triiodothyronine and LBM might slightly contribute to increased energy expenditure in AGHD patients who received GH replacement. Sex hormones affect the secretion and action of GH. In particular, estrogen stimulates GH secretion but inhibits IGF-1 production in the liver [19, 20]. Additionally, it was reported that estrogen also affects energy expenditure [21]. In our study, there
were no patients who received oral estrogen replacement therapy; nevertheless, careful and adequate sex hormone replacement is necessary for patients with AGHD.

LBM increased at 4 and 8 months but not at 12 months. Serum TC and LDL-C levels improved at 4 and 8 months but not at 12 months. In this study, we could not evaluate the individual energy intake; it is important to confirm the intake of calories and evaluate the energy balance according to REE before and after GH treatment. A previous study evaluated the energy balance by using test meal, appetite ratings, REE, and physical activity before and after GH replacement in 19 patients with AGHD [22]. There were no significant changes in the total calorie intake and macronutrient choices before and after GH replacement. In this study, the questionnaire showed that 6 (40.0%) of the enrolled patients had an increase in the appetite after GH replacement. In patients with increased appetite (n = 6), LBM increased by 2.5 kg and LDL-C decreased to 13.3 mg/dL at 12 months; however, in the patients with no change in the appetite (n = 9), LBM increased by 0.7 kg and LDL-C decreased by 15.5 mg/dL at 12 months. Therefore, it might be possible that changes in the appetite after GH replacement affected these improvements. Furthermore, we think it is necessary to elucidate in detail the changes in daily food intake before and after GH replacement. In this study, we observed some adverse effects of GH replacement therapy in 40% of patients, though none were severe. Furthermore, no patients developed diabetes after GH replacement therapy.

The limitations of this study are that the sample size was small and a single-arm, placebo-free design was used. In addition, we could not evaluate the individual food intake before and after GH treatment. Further studies involving a larger sample size should be conducted to establish the overall effectiveness of GH replacement in AGHD.

In summary, GH replacement for 12 months has beneficial effects on the body composition, REE, and segmental lipid metabolism in patients with AGHD.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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Contributors

AM and AH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AH, KT, and MS were responsible for the conception and design of the study and evaluated the data. AM, AH, and KT recruited the patients and collected the data. AM and AH analyzed the data. AM, AH, and MS reviewed the data and were responsible for the final writing and editing of the manuscript.

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