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ORIGINAL

Visceral adipose tissue increases shortly after the cessation of GH therapy in adults with Prader-Willi syndrome

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Abstract. GH therapy in pediatric patients with Prader-Willi syndrome (PWS) improves body composition, but discontinuation of GH after achieving adult height has been implicated in its deterioration. Although there is evidence for the deleterious effects of visceral adipose tissue (VAT) rather than subcutaneous adipose tissue (SAT) on the development of obesity-related complications, the effects of GH discontinuation on fat distribution in adults with PWS has not been fully investigated. Therefore, we utilized dual-energy X-ray absorptiometry (DEXA) and abdominal computed tomography (CT) to compare the fat distribution between before and 6 months or 12 months after the cessation of GH therapy in 7 adult PWS patients. GH therapy was initiated at a mean age of 4.1 ± 1.4 years and discontinued at a mean age of 18.9 ± 1.8 years. Serum IGF-1 levels were decreased by discontinuation of GH therapy. Fat mass was significantly increased 6 and 12 months after GH cessation, whereas muscle mass and bone mineral density were unchanged during both study periods. Abdominal CT analysis revealed that elevations in fat mass were due to increases in VAT rather than SAT. Circulating low-density lipoprotein (LDL) cholesterol levels were significantly elevated 6 months after GH cessation. In conclusion, discontinuation of GH therapy caused rapid increases in visceral adipose tissue and LDL cholesterol levels. These findings indicate that continuation of GH therapy may be a therapeutic option to maintain body composition; however, further studies regarding the long-term benefits and adverse effects of GH therapy in adults with PWS are required.

Key words: Prader-Willi syndrome, Adult, GH therapy, Body composition, Lipid parameters

PRADER-WILLI SYNDROME (PWS) is a genetic disorder resulting from the absence of paternally expressed genes in the 15q11–13 chromosome region due to a deletion, maternal disomy, imprinting defect, or chromosomal translocation; however, the molecular mechanisms by which these genetic abnormalities cause PWS is not fully understood [1, 2]. Clinical characteristics of PWS include neonatal hypotonia, poor feeding during infancy, followed by the development of hyperphagia and obesity. Although hyperphagia is pathogenic to the development of obesity, there is also evidence that alterations in body composition occur before the onset of hyperphagia, suggesting the presence of disease-specific mechanisms that deteriorate body composition in PWS patients [3].

The characteristics of body composition in PWS patients include reduced muscle mass and increased fat mass [4], and these characteristics are similar to those observed in patients with GH deficiency [5, 6]. As in the case with GH deficiency, GH therapy during childhood has been reported to improve body composition in PWS patients [7-11]. Consistent with these observations, the global consensus for GH treatment for PWS states that the main purpose of GH therapy is to improve body composition [12]. Despite these benefits for body composition, GH therapy is not approved after adult height is

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achieved, except for New Zealand. As a result, discontinuation of GH therapy has been implicated in the deterioration of the body composition [13, 14], leading to obesity, diabetes mellitus, respiratory disorders, and cardiopulmonary failure, which are the main causes of death from PWS [15, 16].

There is increasing evidence that visceral adipose tissue (VAT) is more associated with the development of diabetes and dyslipidemia than subcutaneous adipose tissue (SAT) [17-20]; therefore, compartment-specific evaluation of adipose tissue is critical to understand the effects of GH treatment in adult patients with PWS. Although several clinical trials have demonstrated that GH therapy is effective in improving body composition in adult PWS patients, most utilized dual-energy X-ray absorptiometry (DEXA) to evaluate body composition. Although DEXA analysis has been shown to be useful to estimate VAT in PWS adults [21], there is also evidence demonstrating a weak association between DXA-derived VAT and SAT in the general population [22], suggesting that analyzing body composition using DEXA alone may be inadequate to accurately evaluate the fat distribution. To overcome this limitation, we utilized computed tomography (CT) analysis in addition to DEXA for quantification of VAT and SAT to determine the effects of GH discontinuation on fat re-distribution in PWS adults. Although there is evidence demonstrating a trend toward increased VAT mass 12 and 24 months after the cessation of GH therapy by CT analysis [13], the number of studies is quite limited and the effects of GH cessation on fat distribution has never been analyzed in a shorter period. These findings indicate that the exact effects of GH discontinuation on fat re-distribution in PWS adults remain to be determined. Based on these, we explored the alterations in fat distribution 6 and 12 months after GH discontinuation using abdominal CT analysis and found that VAT significantly increased shortly after GH discontinuation.

Materials and Methods

Subjects

We retrospectively evaluated the medical records of PWS patients based on the following inclusion criteria: 1) the diagnosis of PWS was genetically confirmed, 2) GH therapy started during childhood and continued without cessation to adult height, and 3) 12 month had passed since the end of GH therapy. Nine adult PWS patients (four males, and five females) fulfilled the inclusion criteria from November 1981 to March 2017 at Osaka Women's and Children's Hospital. Two patients (one male, and one female) were excluded from the study because DEXA and abdominal CT analyses were not performed. In total, seven adult PWS patients (three males, and four females) were included.

Study design

This study was a single center, retrospective study. We evaluated the data before (baseline), 6 months (n = 7) and 12 months after the cessation of GH therapy (n = 5). Two patients were excluded from 12 months analysis because DEXA analysis was not performed at this point. The baseline data was evaluated 10 ± 6 months before the cessation of GH therapy. Anthropometric measurements included height and weight. Standing height was measured using a digital scale (TANITA DC-250), and height SDS was calculated using normal growth standards for Japanese children based on the year 2000 national survey data [23]. Weight was measured with lightweight clothes on a calibrated scale (TANITA DC-250). BMI was calculated by dividing body weight (kg) by height squared (m^2). Blood pressure was measured with electronic device (TERUMO H55). Body composition, which included fat mass, percent fat mass (%FM: fat mass divided by body mass), muscle mass, and bone mineral parameters, was evaluated by DEXA (Holgic QDR-4500A). Quality control was performed using the Step Phantom scan. Lean body mass (LBM) was determined as body mass minus fat mass, and the skeletal muscle index (SMI) was the mass of the muscle of the upper and lower extremities (kg) divided by the height squared (m^2). Bone mineral parameters included whole body bone mineral density (BMD), lumbar BMD (L2–4), whole body bone mineral content (BMC), and lumbar BMC. The areas of SAT (cm^2), VAT (cm^2) and abdominal girth were measured at the level of the umbilicus by abdominal CT (Toshiba medical system Aquilion ONE). Blood samples were obtained by vein puncture after overnight fasting. Lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride, in the serum were analyzed in five PWS patients (one male, and four females) 6 months after the cessation of GH therapy. One patient was excluded from 12 months study because oral medicine for hyperlipidemia was initiated 6 months after the cessation of GH therapy and therefore, total of four PWS patients (one male, and three females) were included in 12 months study. IGF-1,

HbA1c, fasting blood sugar in the serum were also analyzed. Total cholesterol, HDL cholesterol, and triglyceride levels were measured using DENKA-SEIKEN T-CHO(S) A-N before February 2007 and KYOWA MEDEX Determiner L TC II after March 2007. LDL cholesterol was calculated using the Friedwald formula. IGF-1 levels were measured by an immunoradiometric assay using somatomedin C II SIEMENS before March 2012 and IGF-1 IRMA DAIICHI after April 2012. HbA1c levels were measured by a latex agglutination using DETERMINER HbA1C before March 2013 and measured by high performance liquid chromatography using HLC-723 G9 after April 2013. Dietary energy intake and amount of exercise were evaluated by an interview with the patient and the family by a registered dietitian nutritionist. We also evaluated medications and living environment. This study was approved by the Ethical Committee of Osaka Women's and Children's Hospital (approval No. 1070).

Statistical analysis

Statistical analysis was performed with the paired *t*-test. *P*-values less than 0.05 were considered significant.

Results

Characteristics of subjects

Seven adult PWS patients (three males and four females) were examined (Table 1). All had a deletion in chromosome 15q11–q13. GH therapy was started at a mean age of 4.1 ± 1.4 years and continued for 14.7 ± 2.4 years. GH therapy was ended at 18.9 ± 1.8 years. All were treated with recombinant human GH subcutaneously. The dose of GH was reduced gradually as they reached adult height because the reduced dose has been implicated to be beneficial for maintaining body composition with minimizing the adverse effects in PWS patients [12]. The mean dose of human GH at the time of the cessation of GH therapy was 0.10 mg/kg/week. The mean adult height was 164.6 ± 5.1 cm (–1.0 SDS) in men and 149.1 ± 2.1 cm (–1.6 SDS) in women. No patients developed diabetes mellitus or sleep apnea during GH therapy. Three out of the seven patients had scoliosis, but none exhibited GH treatment-related worsening of scoliosis.

The one patient (Case 2) was prescribed angiotensin-converting enzyme inhibitor for proteinuria and continued taking the medication during the study period. He initiated androgen replacement therapy 6 months after the cessation of GH therapy. The one patient (Case 4)

Table 1 Baseline characteristics of subjects

No.	Sex	Genetic subtype	Age at start of GH (years)	Age at cessation of GH (years)	Duration of GH (years)	Dose of GH at the cessation (mg/kg/week)	Adult height (cm)	Adult height SDS	Scoliosis	Drugs		Job change
										6 months after GH	6 to 12 months after GH	
1	m	deletion	5.2	18.8	13.6	0.055	169.5	–0.2	yes	no	no	no
2	m	deletion	2.5	19.6	17.1	0.081	157.5	–2.3	no	*1	*2	yes
3	m	deletion	3.2	20.2	17.0	0.094	167	–0.7	yes	no	no	no
4	f	deletion	4.7	21.1	16.4	0.081	147	–2.1	no	no	*3	no
5	f	deletion	4.2	15.0	10.8	0.151	147.4	–2.0	no	no	no	*4
6	f	deletion	2.9	19.3	16.3	0.146	150	–1.5	yes	no	no	no
7	f	deletion	6.5	18.2	11.7	0.103	152.3	–1.1	no	no	no	no

m, male; f, female
*1 ACE inhibitor, *2 ACE inhibitor/androgen replacement therapy, *3 statin drug, *4 high school student

initiated the oral medicine for hyperlipidemia 6 months after the cessation of GH therapy. Other patients did not start new medications within the study period.

No remarkable changes in the dietary intake or the amount of exercise were seen during the study period. One patient (Case 5) was a senior high school student at the time of GH discontinuation, and the others worked in facilities for mental retardation. No patients changed their lifestyle during the study period, except for one (Case 2) who changed his workplace, but this did not affect his clinical condition, dietary behaviors, or physical activity.

Discontinuation of GH therapy increased fat mass but did not decrease lean body mass

The anthropometric measurements and DEXA data were compared between baseline and 6 or 12 months after GH discontinuation as shown in Table 2 and Table 3, respectively. All patients increased body weight and BMI (before 24.2 ± 6.5 kg/m^2, after 25.0 ± 6.8 kg/m^2, p = 0.018) 6 months after the GH cessation, and this was associated with significant increases in fat mass (before 20.1 ± 8.1 kg, after 23.3 ± 10.0 kg, p = 0.029) and %FM (before 34.9 ± 7.0%, after 37.2 ± 6.5%, p = 0.002). Of note, LBM, SMI, and bone mineral parameters were not reduced by GH discontinuation during the first 6 months. At 12 months after the cessation of GH therapy, body weight and BMI were not altered compared to baseline data. Although fat mass significantly increased (before 21.1 ± 9.3 kg, after 25.2 ± 9.9 kg, p = 0.043), increases in %FM did not reach statistical significance (before 35.9 ± 7.8%, after 39.1 ± 6.3%, p = 0.090). LBM, SMI, and bone mineral parameters were not reduced by GH discontinuation during the first 12 months.

Visceral fat mass increased 6 months after the cessation of GH therapy

As VAT has been found to exhibit more deleterious effects on lipid metabolism than SAT, we next analyzed the changes in fat distribution by GH cessation and found that the amount of VAT was significantly increased by GH cessation in both study periods as shown in Table 2 and Table 3 (6 months: before 21.8 ± 13.3 cm^2, after 32.2 ± 19.4 cm^2, p = 0.008, 12 months: before 25.2 ± 14.5 cm^2, after 48.0 ± 26.1 cm^2, p = 0.024). The amount of SAT also increased by GH cessation in both study periods, although the difference did not reach statistical significance.

Circulating LDL cholesterol levels were elevated 6 months after the cessation of GH therapy

Serum IGF-1 levels decreased upon GH cessation although the difference between baseline and 12 months after GH cessation did not reach statistical significance (Table 4 and Table 5). Total cholesterol (before 231.2 ± 19.0 mg/dL, after 242.8 ± 18.1 mg/dL, p = 0.033) and LDL cholesterol (before 143.3 ± 16.9 mg/dL, after 156.5 ± 18.1mg/dL, p = 0.010) levels were significantly increased 6 months after the discontinuation of GH therapy, with no changes in neither HDL cholesterol nor triglyceride levels (Table 4). In contrast, lipid parameters 12 months after the discontinuation of GH therapy were not altered compared to baseline data (Table 5). Circulating levels of HbA1c, fasting blood sugar and blood pressure were not altered during both study periods (Table 4 and Table 5). The raw values of parameters in each patient were summarized in Table 6.

Discussion

In the current study, we demonstrated that VAT mass increased 6 and 12 months after the GH discontinuation without affecting muscle mass or bone mineral density. The effect of GH discontinuation on VAT in PWS adults has been previously analyzed, which showed increased VAT mass 12 and 24 months after GH cessation although the difference did not reach statistical significance [13]. In line with this, we found that VAT mass significantly increased after GH cessation and this probably occurred more rapidly than have been reported. Importantly, these changes were accompanied by elevation of LDL cholesterol levels although fasting blood sugar and HbA1c levels were unaffected, suggesting that lipid profiles were more likely affected by the lack of GH therapy in PWS adults. We did not observe increases in lipid profiles 12 months after GH cessation despite increases in VAT mass. This may be caused by the small number of subjects, and the use of androgen replacement therapy in Case 2 since androgen deficiency may have profound effects on body composition in PWS adults [24]. As no changes in medication or lifestyle, including dietary intake, during the first 6 months after the cessation of GH therapy were observed, the deterioration of body composition and lipid profiles during the first 6 months was likely caused by the cessation of GH therapy.

Increases in FM after GH cessation was accompanied by elevations in VAT in PWS adults. Since FM has been shown to increase after the cessation of GH therapy in a

Table 2 Changes in body composition during 6 months after the discontinuation of GH therapy

	Male ($n = 3$)			Female ($n = 4$)			Combined ($n = 7$)		
	at the cessation	6 months after GH	*p*-value	at the cessation	6 months after GH	*p*-value	at the cessation	6 months after GH	*p*-value
Body weight (kg)	72.3 ± 13.1	74.7 ± 13.5	**0.023**	48.6 ± 12.2	49.1 ± 12.3	0.144	59.3 ± 17.3	60.9 ± 17.7	**0.006**
BMI (kg/m^2)	27.4 ± 6.5	27.9 ± 7.0	0.258	22.0 ± 5.5	22.7 ± 5.7	0.069	24.2 ± 6.5	25.0 ± 6.8	**0.018**
abdominal girth (cm)	83.4 ± 10.5*	96.0 ± 13.4*	NA	70.4 ± 7.7	72.1 ± 8.3	0.089	74.7 ± 10.6**	81.0 ± 14.3**	0.081
FM (kg)	26.0 ± 6.5	29.9 ± 8.8	0.255	15.6 ± 6.0	18.3 ± 7.6	0.097	20.1 ± 8.1	23.3 ± 10.0	**0.029**
FM (%)	37.1 ± 6.0	39.1 ± 5.6	0.158	35.9 ± 6.7	35.9 ± 6.7	**0.016**	34.9 ± 7.0	37.2 ± 6.5	**0.002**
LBM (kg)	42.3 ± 3.1	43.8 ± 6.4	0.581	32.2 ± 6.3	31.0 ± 5.0	0.712	36.5 ± 7.2	36.5 ± 8.5	0.991
muscle mass (kg)	33.5 ± 8.0	32.8 ± 7.9	0.191	34.1 ± 6.1	36.9 ± 8.2	0.176	33.9 ± 7.0	35.1 ± 8.4	0.299
BMC of total body (g)	18.7 ± 0.6	19.4 ± 1.0	0.406	13.4 ± 1.9	14.1 ± 1.5	0.35	16.2 ± 2.5	16.8 ± 2.6	0.154
BMD of total body (g/cm^2)	0.96 ± 0.01	0.98 ± 0.02	0.426	0.93 ± 0.01	0.93 ± 0.01	0.682	0.95 ± 0.02	0.96 ± 0.03	0.613
BMC of lumbar spine (g)	35.9 ± 3.7	38.0 ± 1.5	0.441	28.9 ± 6.8	29.7 ± 6.9	0.43	33.3 ± 5.4	34.6 ± 5.5	0.243
BMD of lumbar spine (g/cm^2)	0.83 ± 0.05	0.82 ± 0.06	0.282	0.81 ± 0.09	0.823 ± 0.08	0.069	0.83 ± 0.06	0.82 ± 0.06	0.856
SMI (kg/m^2)	6.5 ± 0.9	6.6 ± 1.4	0.815	4.8 ± 0.5	4.7 ± 0.6	0.821	5.7 ± 1.0	5.8 ± 1.2	0.707
visceral fat (cm^2)	26.5 ± 14.6	40.4 ± 22.7	0.135	18.4 ± 11.1	26.0 ± 13.6	**0.021**	21.8 ± 13.3	32.2 ± 19.4	**0.008**
subcutaneous fat (cm^2)	247.1 ± 73.8	282.8 ± 57.3	0.248	138.6 ± 73.6	149.5 ± 77.2	**0.019**	185.1 ± 91.9	206.6 ± 95.7	0.071

* $n = 2$, ** $n = 6$

All values are expressed as mean ± SD

The *p*-values are bold where they are less than 0.05.

BMI, body mass index; FM, fat mass; LBM, lean body mass; BMC, bone mineral content; BMD, bone mineral density; SMI, skeletal mass index; NA, not available

Table 3 Changes in body composition during 12 months after the discontinuation of GH therapy

	Male (n = 2)			Female (n = 3)			Combined (n = 5)		
	at the cessation	12 months after GH	p-value	at the cessation	12 months after GH	p-value	at the cessation	12 months after GH	p-value
Body weight (kg)	80.9 ± 8.6	80.2 ± 7.4	NA	47.7 ± 13.8	50.5 ± 13.4	**0.015**	61.0 ± 20.2	62.4 ± 18.5	0.207
BMI (kg/m^2)	30.6 ± 5.2	30.3 ± 5.0	NA	21.7 ± 6.3	23.0 ± 6.3	**0.008**	25.3 ± 7.3	25.6 ± 6.8	0.200
abdominal girth (cm)	94*	107.1*	NA	70.2 ± 8.9	77.9 ± 13.9	0.182	76.1 ± 12.8**	85.2 ± 17.4**	0.058
FM (kg)	30.6 ± 0.8	33.6 ± 1.4	NA	14.7 ± 6.7	19.5 ± 9.1	0.141	21.1 ± 9.3	25.2 ± 9.9	**0.043**
FM (%)	41.2 ± 2.2	42.4 ± 2.1	NA	32.4 ± 8.2	37.0 ± 7.2	0.164	35.9 ± 7.8	39.1 ± 6.3	0.090
LBM (kg)	42.9 ± 3.7	46.0 ± 5.9	NA	32.0 ± 7.2	30.8 ± 4.8	0.782	36.4 ± 8.1	36.9 ± 9.1	0.861
muscle mass (kg)	30.6 ± 8.5	30.6 ± 7.5	NA	35.2 ± 6.7	38.8 ± 7.8	0.385	33.4 ± 7.8	35.5 ± 8.7	0.127
BMC of total body (g)	18.9 ± 0.6	19.6 ± 0.6	NA	13.9 ± 1.7	14.6 ± 1.3	0.568	15.9 ± 2.8	16.6 ± 2.7	0.106
BMD of total body (g/cm^2)	0.98 ± 0.01	1.00 ± 0.02	NA	0.94 ± 0.03	0.92 ± 0.04	0.115	0.95 ± 0.03	0.95 ± 0.05	0.974
BMC of lumbar spine (g)	38.2 ± 2.3	37.0 ± 1.3	NA	29.7 ± 5.7	30.8 ± 6.2	0.861	33.1 ± 6.2	33.2 ± 5.7	0.867
BMD of lumbar spine (g/cm^2)	0.87 ± 0.01	0.89 ± 0.05	NA	0.81 ± 0.07	0.81 ± 0.08	0.54	0.83 ± 0.06	0.84 ± 0.08	0.672
SMI (kg/m^2)	6.7 ± 1.1	6.5 ± 1.0	NA	5.0 ± 0.5	5.4 ± 1.1	0.463	5.7 ± 1.1	5.8 ± 1.2	0.610
visceral fat (cm^2)	33.8 ± 12.8	55.4 ± 22.3	NA	19.4 ± 12.6	43.1 ± 27.3	0.153	25.2 ± 14.5	48.0 ± 26.1	**0.024**
subcutaneous fat (cm^2)	299.2 ± 6.9	325.5 ± 50.4	NA	138.3 ± 85.0	205.8 ± 128.2	0.172	202.6 ± 102.7	253.6 ± 119.6	0.106

* n = 1, ** n = 4

All values are expressed as mean ± SD

The p-values are bold where they are less than 0.05.

BMI, body mass index; FM, fat mass; LBM, lean body mass; BMC, bone mineral content; BMD, bone mineral density; SMI, skeletal mass index; NA, not available

Table 4 Changes in blood and physical examination 6 months after the discontinuation of GH therapy

	at the cessation of GH	6 months after GH	*p*-value
Total cholesterol (mg/dL)*	231.2 ± 19.0	242.8 ± 18.1	**0.033**
LDL cholesterol (mg/dL)*	143.3 ± 16.9	156.5 ± 18.1	**0.010**
HDL cholesterol (mg/dL)*	60.8 ± 17.0	59.6 ± 10.4	0.852
TG (mg/dL)*	80.8 ± 33.1	106.4 ± 35.1	0.332
IGF-1 (ng/mL)**	448.5 ± 185.3	227.9 ± 65.0	**0.025**
HbA1c (%)***	5.7 ± 0.5	5.6 ± 0.5	0.422
Fasting blood sugar (mg/dL)	93.2 ± 8.7	86.1 ± 9.4	0.080
Systolic BP (mmHg)	109.2 ± 10.9	102.8 ± 7.3	0.155
Diastolic BP (mmHg)	67.2 ± 11.4	71.4 ± 9.4	0.232

* in five PWS patients (one male, four females)
** in six PWS patients (two males, three females)
*** in four PWS patients (one male, three females)
All values are expressed as mean ± SD
The *p*-values are bold where they are less than 0.05.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; BP, blood pressure

Table 5 Changes in blood and physical examination 12 months after the discontinuation of GH therapy

	at the cessation of GH	12 months after GH	*p*-value
Total cholesterol (mg/dL)*	222.0 ± 5.5	237.5 ± 18.1	0.273
LDL cholesterol (mg/dL)*	136.2 ± 10.0	149.4 ± 18.1	0.264
HDL cholesterol (mg/dL)*	54.5 ± 12.8	58.5 ± 10.4	0.627
TG (mg/dL)*	89.5 ± 31.5	115.8 ± 35.1	0.163
IGF-1 (ng/mL)**	412.3 ± 182.6	182.0 ± 19.9	0.066
HbA1c (%)***	5.6 ± 0.5	5.7 ± 0.5	0.836
Fasting blood sugar (mg/dL)	93.2 ± 8.7	88.6 ± 9.4	0.060
Systolic BP (mmHg)	109.2 ± 10.9	110.7 ± 7.3	0.697
Diastolic BP (mmHg)	67.2 ± 11.4	69.4 ± 9.4	0.565

* in four PWS patients (one male, three females)
** in five PWS patients (two males, three females)
*** in four PWS patients (one male, three females)
All values are expressed as mean ± SD
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; BP, blood pressure

short period in young adults who were severe GH deficiency or born small-for-gestational age [25-28], increases in FM after GH cessation is not likely unique to PWS patients. Consistent with this, lipid parameters have been shown to deteriorate after discontinuation of GH therapy in adolescents with GH deficiency, Turner syndrome or born small-for-gestational age [29]. Higher VAT mass has been implicated in the reduced secretion of insulin-sensitizing adiponectin and increased secretion of inflammatory cytokines such as TNF-α and IL-6 [30]. Adipokines, such as adiponectin, are also implicated in PWS in that the level of adiponectin decreases as VAT increases [31]. Indeed, adiponectin levels are lower in non-GH-treated PWS patients than in GH treated PWS patients [32]. As total cholesterol and LDL cholesterol levels have been found to be negatively correlated with adiponectin in PWS [31], the deterioration in lipid profiles seen in our study may be due to the changes in

Table 6 The raw values of parameters in each PWS patient

No.	Sex	Body weight (kg)			BMI (kg/m^2)			Abdominal girth (cm)			Fat mass (kg)			Fat mass (%)			Visceral fat (cm^2)			Subcutaneous fat (cm^2)		
		Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo
1	m	72.3	74.7	72.8	25.4	25.4	25.3	NA	NA	NA	31.5	33.3	32.2	43.5	43.8	44.5	21	32.1	33.1	292.3	285.7	275.1
2	m	89.5	91.8	87.7	36.0	37.6	35.4	94	109.4	107.1	29.8	38.7	35.1	39	42.3	40.3	46.6	71.5	77.7	306.1	351.6	375.9
3	m	57.3	58.7	58.1	20.4	20.9	20.8	72.9	82.6	NA	16.8	17.9	NA	29	31.2	NA	11.9	17.6	NA	143.1	211.2	NA
4	f	66.2	68	68.3	30.4	31.6	31.6	82.8	85.4	96.9	24.2	30.4	32.4	43.2	45.7	47.3	37.3	48.6	80.8	258.5	274.9	386
5	f	32.8	34.9	35.7	15.3	16.2	16.4	63.1	63.1	64	10.4	11.9	11.5	30.9	34.3	32.1	9.08	13.9	16.8	81.49	86.6	98.2
6	f	44.2	43.6	47.5	19.6	19.7	21.1	64.8	67.8	72.8	9.6	11.5	14.9	23.1	26.7	31.7	12.1	16.6	31.8	75	84.8	133.2
7	f	53.1	54.6	55.3	23.0	23.5	23.8	71.1	72.3	NA	18.3	19.7	NA	35.8	37	NA	15.2	25.1	NA	139.6	151.7	NA

No.	Sex	Lean body mass (kg)			Muscle mass (kg)			BMC of total body (g)			BMD of total body (g/cm^2)			BMC of lumbar spine (g)			BMD of lumbar spine (g/cm^2)			Skeletal mass index (kg/m^2)		
		Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo
1	m	39.2	39.1	40.1	39.2	39.1	38.2	18.3	20.3	19.0	0.966	1.015	0.974	40.6	NA	38.4	0.868	0.873	0.836	5.6	5.4	5.5
2	m	46.7	53.0	52.0	22.2	21.5	23.0	19.6	19.9	20.3	0.994	0.99	1.033	35.9	36.3	35.7	0.889	0.868	0.952	7.9	8.6	7.7
3	m	41.1	39.6	NA	39.3	37.8	NA	18.2	18.0	NA	0.948	0.952	NA	31.3	37.8	NA	0.759	0.733	NA	6.1	5.8	NA
4	f	31.8	36.1	36.0	30.3	34.7	34.6	15.2	14.6	14.7	0.966	0.936	0.901	31.6	30.5	33.1	0.818	0.822	0.8	5.5	5.9	6.8
5	f	23.3	22.8	24.3	44.8	51.0	49.9	11.5	12.5	12.9	0.896	0.901	0.895	22.0	22.7	22.3	0.718	0.735	0.72	4.3	4.1	3.9
6	f	41.2	31.6	32.1	30.6	30.1	32.1	15.3	15.6	16.2	0.97	0.97	0.986	35.8	36.7	37.1	0.901	0.91	0.924	5.4	5.3	5.5
7	f	32.8	33.7	NA	31.2	32.0	NA	16.0	16.7	NA	0.956	0.965	NA	36.2	38.1	NA	0.859	0.863	NA	5.5	5.6	NA

No.	Sex	Total cholesterol (mg/dL)			LDL cholesterol (mg/dL)			HDL cholesterol (mg/dL)			TG (mg/dL)			IFG-1 (ng/mL)			HbA1C (%)			Fasting blood sugar (mg/dL)			Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
		Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo	Pre	6Mo	12Mo
1	m	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	295.4	217.9	171.9	NA	NA	NA	79	84	85	114	96	112	57	68	61
2	m	216	219	250	127	149	162	53	49	46	142	129	193	629.3	362	NA	NA	NA	NA	99	102	94	111	106	113	71	86	91
3	m	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	300	211	216	5.9	5.8	5.8	97	89	94	110	110	113	61	68	65
4	f	268	275	250	172	185	169	86	65	66	46	163	67	774.7	234.3	184.3	4.7	4.7	4.8	91	77	87	124	116	135	92	84	94
5	f	220	237	217	127.2	132.6	121.4	34	47	38	86	95	88	332.3	155.1	155	NA	NA	NA	90	87	82	85	98	99	55	58	49
6	f	231	239	225	139	148	139	65	75	90	67	76	68	359	187	183	6.2	6.3	6.5	109	93	99	109	96	104	66	72	66
7	f	221	244	258	151.4	168.2	175.2	66	62	60	63	69	114	NA	NA	NA	5.9	5.5	5.7	88	71	79	112	98	99	69	64	60

Pre: at the cessation of GH, 6Mo: 6 months after GH cessastion, 12Mo: 12 months after GH cessation

BMI, body mass index; FM, fat mass; LBM, lean body mass; BMC, bone mineral content; BMD, bone mineral density; SMI, skeletal mass index; NA, not available

adipocytokines. Furthermore, as increased VAT is associated with obstructive sleep apnea syndrome [33], one of the causes of death in PWS adults, maintaining an appropriate body composition by continuation of GH therapy from childhood to adulthood is important to maintain a higher quality of life (QOL) in adult PWS patients.

GH therapy improves body composition and lipid profiles both in children [34-44] and adults PWS patients [45-52]; therefore, continuation of GH therapy after adult height is achieved may be beneficial for maintaining body composition, which eventually reduces the risk of obesity-related complications in adults with PWS. However, GH therapy for PWS adults has not been approved globally, except for New Zealand. In addition, there are no reports regarding the adverse effects of long-term use of GH during adulthood. As long-term use of GH during childhood has been reported to not increase the risk of complications, such as glucose metabolism [53], respiratory disorders [54] and scoliosis [55], GH may also be safely administered and the benefits may outweigh the demerits in adult PWS patients, but further studies are required to unravel the long-term safety issues regarding GH treatment in adult PWS.

Although LBM has been reported to decrease within one year after the cessation of GH therapy [14], this parameter was maintained in our study, probably because all subjects maintained their exercise habits during the study period such as taking a walk daily or swimming lesson once a week. However, it is still possible that LBM could decrease if the subjects were monitored for a longer period.

Our study has the following limitations. First, this was a single center, retrospective study and the sample size was small. Second, we did not evaluate physical activity or food intake in a quantitative manner. Third, we did not analyze GH secretion by GH provocation test after GH discontinuation. Fourth, we did not analyze adipocytokines and insulin levels. Fifth, we did not measure waist/hip ratio as a marker for visceral obesity. Further prospective analyses, including quantitative evaluation of physical activity and food intake and GH provocation test, are required to overcome these limitations.

In conclusion, the cessation of GH therapy in PWS patients caused rapid increases in VAT. As increased VAT is associated with an increased risk of dyslipidemia and obstructive sleep apnea, continuation of GH therapy after adult height is achieved may be a therapeutic option to maintain a higher QOL in adult PWS patients. However, the long-term benefits and adverse effects of GH therapy for PWS adults are unclear and further analyses are required.

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Disclosure

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

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