Clinical Research Article

Effects of Growth Hormone Treatment on Sleep-Related Parameters in Adults With Prader-Willi Syndrome

Hasanain Hamid Shukur,1 Laith Hussain-Alkhateeb,2 Stense Farholt,3 Ole Nørregaard,4 Anders Palmstrøm Jørgensen,5 and Charlotte Hoybye1,6

1Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Solna SE-171 76, Sweden; 2Global Health, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 40530 Gothenburg, Sweden; 3Center for Rare Diseases, Department of Pediatric and Adolescent Medicine, Aarhus University Hospital, DK-8200 Aarhus N, Denmark; 4Danish Respiratory Center West, Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, DK-8200 Aarhus N, Denmark; 5Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital, Rikshospitalet, 0424 Oslo, Norway; and 6Department of Endocrinology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

ORCID numbers: 0000-0003-3265-9566 (H. H. Shukur); 0000-0001-9607-110X (L. Hussain-Alkhateeb); 0000-0002-5013-7078 (S. Farholt); 0000-0002-1246-9194 (A. P. Jørgensen); 0000-0002-3980-1927 (C. Hoybye).

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; ENT, ear, nose, and throat; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnographic; PWS, Prader-Willi syndrome; REM, rapid eye movement; SaO₂%, oxygen saturation percentage; SE, sleep efficiency; SRBDs, sleep-related breathing disorders.

Received: 9 February 2021; Editorial Decision: 28 April 2021; First Published Online: 5 May 2021; Corrected and Typeset: 5 June 2021.

Abstract

Context: Prader-Willi syndrome (PWS) is a rare, genetic, multisymptom, neurodevelopmental disease due to lack of the expression of the paternal genes in the q11 to q13 region of chromosome 15. The main characteristics of PWS are muscular hypotonia, hyperphagia, obesity, behavioral problems, cognitive disabilities, and endocrine deficiencies, including growth hormone (GH) deficiency. Sleep apnea and abnormal sleep patterns are common in PWS. GH treatment might theoretically have a negative impact on respiration.

Objective: Here we present the effect of GH treatment on polysomnographic measurements.

Methods: Thirty-seven adults, 15 men and 22 women, with confirmed PWS were randomly assigned to 1 year of GH treatment (n = 19) or placebo (n = 18) followed by 2 years of GH treatment to all. Polysomnographic measurements were performed every
6 months. A mixed-effect regression model was used for comparison over time in the subgroup that received GH for 3 years.

**Results:** At baseline median age was 29.5 years, body mass index 27.1, insulin-like growth factor 115 µg/L, apnea-hypopnea index (AHI) 1.4 (range, 0.0-13.9), and sleep efficiency (SE) 89.0% (range, 41.0%-99.0%). No differences in sleep or respiratory parameters were seen between GH- and placebo-treated patients. SE continuously improved throughout the study, also after adjustment for BMI, and the length of the longest apnea increased. AHI inconsistently increased within normal range.

**Conclusion:** SE improved during GH treatment and no clinical, significantly negative impact on respiration was seen. The etiology of breathing disorders is multifactorial and awareness of them should always be present in adults with PWS with or without GH treatment.

**Key Words:** Prader-Willi syndrome, GH treatment, polysomnography, sleep-related breathing disorders

---

Prader-Willi syndrome (PWS, OMIM 176270) is a rare genetic disease with an incidence of about 1 in 15 000 children (1, 2). PWS is caused by the lack of expression of the paternal genes in the q11 to q13 region of chromosome 15, caused by deletion, maternal disomy, imprinting defects, or translocations (1, 2). In adults, PWS is clinically characterized by muscular hypotonia, short stature, hyperphagia with high risk of severe obesity, endocrine deficiencies, behavioral problems, and cognitive dysfunction (1-3). Body composition in PWS is abnormal, with an increased fat mass and low lean body mass, even without obesity (1-3). Low growth hormone (GH) levels are common, and several studies of GH treatment in adults have consistently reported improved body composition as well as beneficial effects in physical capacity and quality of life (1-4).

Sleep-related breathing disorders (SRBDs) and hypersomnolence are frequent in PWS (5). The prevalence of obstructive sleep apnea (OSA) in children with PWS has been reported to be as high as 80% (6) and the prevalence of moderate to severe OSA to be 22% in adults with PWS (8). SRBDs are probably caused by a combination of peripheral and central factors consisting of reduced central chemoreceptor sensitivity to hypoxia and hypercapnia, together with several peripheral factors like obesity, muscular hypotonia, craniofacial abnormalities, and adenotonsillar hypertrophy (5-7). In addition, there might be an alteration in the central ventilatory regulation during stress (9). SRBDs include central and obstructive apnea and hypopnea. Central apnea is predominantly seen in infants with PWS, whereas OSA is seen among older and obese children and adults with PWS (5-7). Owing to the frequently present behavioral problems, treatment of OSA with continuous positive airway pressure (CPAP) can be a challenge. Excessive daytime sleepiness can be one of the consequences of OSA; however, it can have other etiologies, and may continue even after OSA is treated.

Severe obesity, adenotonsillar hypertrophy, or intercurrent respiratory tract infection can exacerbate OSA and may even lead to sudden death (4, 5, 10-16). High levels of insulin-like growth factor 1 (IGF-1) generated by GH treatment might stimulate growth of lymphoid tissue (4, 7). Although a relation between GH treatment and increased risk of death is not evidenced, there are speculations about potential associations between GH therapy and unexpected death in children (4, 5, 10-16). However, a recent review concluded that GH can be safely administered in children with PWS, provided that SRBDs are monitored and treated appropriately (5). By themselves, SRBDs are associated with increased cardiovascular and respiratory morbidity (17). There is limited information on SRBDs in adults with PWS and especially in relation to GH treatment. Here we present polysomnographic (PSG) results from a 1-year, double-blind, randomized, placebo-controlled trial followed by an open GH treatment period for 2 years. The aims of this study were to evaluate the effect of short- and long-term GH treatment on respiratory and sleep parameters. Based on our clinical experience and previous studies, we hypothesized that GH treatment would unlikely impair breathing or sleep parameters.

**Material and Methods**

**Patients**

This study was part of the Scandinavian study on GH treatment in adults with PWS (18-20), which was an investigator-initiated trial with a 1-year, randomized, placebo-controlled period, followed by a 2-year, open-phase GH treatment period (Figure 1). The study took place between 2005 and 2010. In total 42 adults with PWS (21 women) with genetically verified PWS completed the trial. GH secretion was evaluated with the GH-releasing hormone-arginine stimulation
test. The median peak GH response was 16.7 μg/L (range, 5.95-44.55 μg/L), and 6 patients fulfilled the body mass index (BMI)-related cutoff limits for severe GH deficiency (GHD) (19). For the present study 5 patients were excluded: 2 patients because of lack of data, 1 patient continued to grow, 1 patient left the study after the first visit, and 1 patient dropped out because of a 10-kg increase in body weight during the study period. Thus 37 patients were retained. Most were GH treatment naive. A few participants were treated with GH during childhood, but they had been off GH treatment for at least 1 year before enrollment in this study. None had received GH therapy in adulthood. An informed consent, signed both by the patients and their legal guardians, was obligatory before inclusion.

The placebo-controlled period was double-blinded. During the first 4 weeks the patients were treated with either GH or placebo, 0.3 mg/day or 0.4 mg/day if body weight was below or above 100 kg. Thereafter doses were increased to 0.6 mg/day or 0.8 mg/day, respectively, and maintained fixed for the following 11 months. During the open phase the GH dose was titrated according to IGF-1 levels of age-matched controls. A group of independent physicians monitored the safety throughout the study. The study was approved by the independent regional ethical committees (Stockholm D No. 03-448, Aarhus D No. 20040072 and Oslo S No. 04205) and registered with clinical trial registration number NCT00372125).

Data for the present study were collected from visits at baseline and every sixth month thereafter. The data included height, weight, BMI, and IGF-1. Results from PSG recordings, included oxygen saturation percentage (SaO₂%), number of desaturations, apneas, and hypopneas, as well as apnea-hypopnea index (AHI), longest apnea, longest hypopnea, and periodic leg movements (PLMs). Variables on sleep quality included wakefulness duration, total sleep duration, rapid eye movement (REM) percentage, REM latency, sleep efficiency (SE) percentage, and delta sleep.

In addition, patients underwent an ear, nose, and throat (ENT) examination at baseline to exclude tonsillar hypertrophy or other significant upper airway obstructions, which would exclude starting in the study. The ENT examinations were repeated every 12 months.

**Measurements**

Standing height was measured with a calibrated Harpenden stadiometer, weight was determined on a calibrated scale and BMI was calculated as weight in kilograms divided by squared height in meters (kg/m²). All PSGs were evaluated and scored by doctors experienced with the interpretation and international criteria for the recording and scoring of sleep (21-24). Chest and abdominal wall movements were recorded by plethysmographic strain belts. Multiple parameters were recorded simultaneously. SaO₂% was continuously measured by pulse oximetry. An apnea was defined as a reduction in airflow of 90% or more during at least 10 seconds and was considered central if the respiratory event was associated with absent breathing effort for 10 seconds or more with an arousal or a decrease in SaO₂% of at least 3%. Hypopneas were defined as a reduction of airflow of at least 30% for 10 seconds or more, with a decrease in SaO₂% of at least 3% or an arousal. The number of apneas and hypopneas were counted during the total sleep time and AHI was calculated per hour of sleep. Throughout sleep, intervals of REM sleep typically occur every 90 to 120 minutes and normally constitute 20% to 25% of sleep. REM latency was defined as the time from the sleep onset to the first period of REM sleep (normal duration, 50-150 minutes). SE was calculated by dividing the total sleep time by the total time in bed, multiplied by 100; 85% or above represents normal SE, and greater than 90% represents very good SE, with 100% indicating that the patient is not getting enough sleep time. Delta sleep is defined as the deepest form of sleep, which declines with age; it is thought that tissue repair and regeneration occur most efficiently during delta sleep. Finally, apnea severity was defined according to current criteria of the American Academy of Sleep Medicine as follows: nonapnea; AHI less than 5, mild apnea; AHI greater than or equal to 5 but less than 15, moderate apnea; AHI less than or equal to 15 but less than 30, and severe apnea; AHI = 30 or greater (21).

**Blood Samples**

IGF-1 was analyzed centrally with a time-resolved immunofluorometric in-house assay with an intervariation less than 10% (25). Throughout the study glucose metabolism, blood lipids and blood pressure were monitored (data not shown) (18-20).
Statistics

Owing to the multitude of data from the PSGs, a principal component analysis was performed to refine the existing dimensions in the data. Factor loadings for the varimax orthogonal rotation with a cutoff of 0.6 were used to retain the model factors. From this AHI, longest apnea, SaO₂%, number of desaturations, REM%, sleep efficiency, PLM, REM latency, and delta sleep were identified as the 9 outcomes best representing distinguishable dimensions in the data set. For the analyses of sleep parameters, a relation between BMI and body fat was surmised and detailed calculations with different body composition parameters were not performed.

Descriptive and analytical statistics were performed and, because of the nonparametric nature of the outcomes, results were expressed as median and range (minimum to maximum). Baseline data were compared between the GH- and placebo-treated groups using the Mann-Whitney test (Table 1). In the patients treated with GH from baseline to 36 months, crude and a BMI-adjusted repeated measures mixed-effect linear regression model were used to investigate the association between the follow-up interval period (ie, 6, 12, 18, 24, 30, and 36 months) and each of the 9 outcomes (AHI, longest apnea, SaO₂%, number of desaturations, REM%, SE, PLM, delta sleep, and REM latency).

A P value less than .05 was defined as statistical significance. All statistical tests were performed using STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC).

Results

Baseline Characteristics

The median age of the participants was 29.5 years (range, 16.0-41.6 years). They were overweight (BMI 27.1 [range, 17.9-44.8]) and IGF-1 was low (115 µg/L [range, 61.0-185.0 µg/L]). SE was normal (89.0% [range, 41.0%-99.0%]) and AHIs (1.4 [range, 0.0-13.9]) were observed. Nineteen (51%) (7 male and 12 female) patients were randomly assigned to GH treatment, and 18 (49%) (8 male and 10 female) to placebo treatment. No differences were noted between the 2 groups (see Table 1). At baseline, 34 patients had no apnea (AHI < 5), 3 had mild (AHI 5 < 15), and no patient suffered from moderate (AHI 15 < 30) or severe apnea (AHI > 30).

Comparison Between Placebo- and GH-Treated Group at 1 Year

At year 1 IGF-1 had increased to 165 µg/L (range, 69-257 µg/L) in the GH-treated group, whereas it was unchanged in the placebo group (P = .013). No significant differences were seen between GH and placebo treatment on the respiration or sleep parameters identified in the principal component analysis (Table 2).

---

**Table 1. Baseline characteristics for 37 adults with Prader-Willi Syndrome (PWS) presented as median (minimum to maximum)**

|                     | Placebo (n = 18) | Growth hormone (n = 19) | P*       | Total (n = 37) |
|---------------------|------------------|------------------------|----------|---------------|
| BMI                 | 27.0 (17.9-41.9) | 27.3 (19.9-44.8)       | .776     | 27.1 (17.9-44.8) |
| Age, y              | 29.6 (17.8-41.6) | 27.2 (16.0-39.4)       | .573     | 29.5 (16.0-41.6) |
| AHI                 | 1.2 (0.0-12.8)   | 1.4 (0.0-13.9)         | .644     | 1.4 (0.0-13.9)  |
| Sleep efficiency, % | 89.0 (41.0-99.0) | 89.0 (53.0-97.0)       | .689     | 89.0 (41.0-99.0) |
| REM, %              | 11.7 (0.0-39.4)  | 19.9 (4.0-53.0)        | .035     | 17.0 (0.0-53.0)  |
| REM latency, min    | 35.5 (0.5-372.0) | 56.0 (1.0-121.0)       | .586     | 40.0 (0.5-372.0) |
| PLM                 | 44.0 (0.0-231.0) | 24.0 (0.0-257.0)       | .290     | 34.5 (0.0-257.0) |
| No. of desaturations, total | 13 (2-143) | 23 (4-232) | .657 | 19 (2-232) |
| SAT, %              | 96 (92-97)       | 96 (91-98)             | .735     | 112 (61-185)    |
| IGF-1, µg/L         | 104 (66-186)     | 116 (61-174)           | .702     | 115 (61.0-186)  |
| No. of apnea        | 0.2 (0.0-91.0)   | 0.1 (0.0-3.6)          | .313     | 0.2 (0.0-91.0)  |
| No. of hypopnea     | 1.2 (0.1-8.9)    | 0.4 (0.0-10.2)         | .499     | 0.8 (0.0-10.2)  |
| Longest apnea, sec  | 17.3 (0.0-77.0)  | 19.0 (0.0-67.9)        | .603     | 18.2 (0.0-77.0) |
| Longest hypopnea, sec | 32.9 (23.2-121.8) | 60.1 (0.0-112.3) | .604 | 36.7 (0.0-121.8) |
| Wakefulness duration, min | 49.5 (6.0-251.0) | 45.0 (8.0-132.0) | .437 | 47.8 (6.0-251.0) |
| Total sleep duration, min | 480.0 (256.0-534.0) | 461.0 (140.0-501.0) | .518 | 473.0 (140.0-534.0) |
| Delta sleep         | 24.4 (3.7-52.5)  | 19.1 (4.0-26.6)        | .112     | 22.3 (3.7-52.5) |

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; IGF-1, insulin-like growth factor 1; PLM, periodic limb movement; REM, rapid eye movement; SAT, oxygen saturation.

*Mann-Whitney test.
Effect of Long-Term Growth Hormone Treatment

In patients who received GH from baseline to 36 months, IGF-1 increased from 104 µg/L (range, 66-186 µg/L) to 178 µg/L (range, 113-295 µg/L). Median SE at year 3 had increased to 91% (range, 57%-100%), P value equal to .001; however, a trend to toward a higher AHI was also observed; 2.4 (range, 0.0-52.9), P value equal to .105. No other changes were seen in the clinical characteristics nor in the respiratory or sleep parameters.

Compared to baseline, the mixed-effect regression model showed an increase in AHI over time but with an intermittently significant association (Table 3). Adjusting for BMI did not change the results (see Table 3). The number of desaturations also inconsistently increased, even after adjustment for BMI, while the length of the longest apnea was significantly increased at the last visit and after adjustment for BMI.

SE increased throughout the study, starting from the 6-month visit and with consistent statistical significance, even after adjustment for BMI, while all other parameters remained unchanged (see Table 3).

None of the participants died during the study period.

Continuous Positive Airway Pressure and Ear, Nose, and Throat Examinations

Five patients were treated with CPAP for sleep apnea at the study start. Two of them, who were assigned to GH treatment from baseline, were still on CPAP by the end of the study, whereas the other 3 patients, who were assigned to placebo treatment at baseline, discontinued CPAP treatment after 6 months or 1 year. During the study one patient (from the placebo group) began CPAP treatment for a short time period because of an already existing sleep apnea.

At baseline the ENT examination showed tonsillar hypertrophy in 4 patients in the placebo and 1 patient in the GH treatment group. Two of them underwent tonsillectomy. At year 1, a cleft palate operation was performed in 1 patient in the GH treatment group, whereas no ENT abnormality was seen in any patient at the 2- or 3-year follow-up. The aforementioned abnormal ENT findings did not have a significant effect on the PSG measurements (data not shown).

Discussion

This 1-year, randomized, placebo-controlled GH study followed by a 2-year, open-phase GH treatment period investigated the effect of GH on respiration and sleep parameters in adults with PWS. No differences were seen between placebo and GH treatment. SE increased during 3 years of continuous GH treatment, even after adjustment for BMI. Median AHI was normal at baseline and did not increase significantly, whereas the length of the longest apnea inconsistently increased during the study, and no significant association between the longest apnea and desaturation was seen. Therefore, the increase in the longest apneas was not assessed to be of clinical significance. No other effects of GH treatment on respiration and sleep parameters during short- or long-term treatment were observed.

The estimated mortality risk for individuals with PWS is high and has been reported to be as high as 3% per year across all age groups (10-16). Respiratory disease is a frequent cause of death, including cases of sudden death (10-16). The risk of developing sleep apnea during GH therapy is of concern because of previous reports of sudden death in children with PWS on GH treatment. This association was highlighted in 2003, when the US Federal Drug
Table 3. Mixed-effect regression model assessing the association of 8 outcomes by 36 months’ treatment with growth hormone, crude- and body mass index–adjusted for (n = 19)

| Outcome                  | Follow-up periods, mo | Coef (95% CI) | P     | Coef (95% CI) | P     |
|--------------------------|-----------------------|---------------|-------|---------------|-------|
|                          |                       | Crude         |       | BMI-adjusted  |       |
| AHI                      | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | −0.004 (−2.38 to 2.37) | .997 | −0.38 (−2.70 to 1.95) | .751 |
| 12                       |                       | 1.56 (−0.82 to 3.93)  | .200 | 1.003 (−1.34 to 3.34) | .400 |
| 18                       |                       | 3.03 (0.65 to 5.41)  | .048 | 2.77 (0.42 to 5.12)  | .021 |
| 24                       |                       | 2.94 (0.57 to 5.32)  | .015 | 2.36 (0.31 to 4.96)  | .026 |
| 30                       |                       | 2.55 (0.09 to 5.01)  | .042 | 2.55 (0.14 to 4.96)  | .038 |
| 36                       |                       | 2.19 (−0.33 to 4.77) | .097 | 2.12 (−0.44 to 4.68) | .105 |
| Longest apnea, sec       | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | 0.67 (−8.67 to 10.01) | .888 | 0.74 (−8.64 to 10.122) | .877 |
| 12                       |                       | −2.38 (−11.64 to 6.78) | .614 | −2.29 (−11.60 to 7.03) | .630 |
| 18                       |                       | 5.10 (−4.07 to 14.28) | .276 | 5.23 (−4.05 to 14.52) | .270 |
| 24                       |                       | 6.74 (−2.51 to 16.00) | .153 | 6.79 (−2.50 to 16.08) | .152 |
| 30                       |                       | 8.32 (−1.22 to 17.85) | .087 | 8.35 (−1.21 to 17.92) | .087 |
| 36                       |                       | 11.58 (1.43 to 21.71) | .825 | 11.62 (1.45 to 21.79) | .025 |
| PLM                      | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | −9.71 (−34.70 to 15.29) | .447 | −9.52 (−34.62 to 15.58) | .475 |
| 12                       |                       | −4.85 (−29.69 to 20.00) | .702 | 4.43 (−29.39 to 20.53) | .728 |
| 18                       |                       | 11.84 (−12.81 to 36.48) | .347 | 12.24 (−12.69 to 37.19) | .336 |
| 24                       |                       | 12.26 (−12.41 to 36.92) | .330 | 12.38 (−12.39 to 37.14) | .327 |
| 30                       |                       | 25.89 (0.43 to 51.35)  | .046 | 25.85 (0.28 to 51.41)  | .048 |
| 36                       |                       | 20.60 (−5.92 to 47.13) | .128 | 21.81 (−5.13 to 48.75) | .113 |
| SAT, %                   | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | 2.82 (−0.58 to 6.16)  | .097 | 2.91 (−0.44 to 6.25)  | .089 |
| 12                       |                       | −0.54 (−3.88 to 2.79)  | .749 | −0.43 (−3.78 to 2.92)  | .803 |
| 18                       |                       | −1.72 (−5.04 to 1.61)  | .312 | −1.73 (−5.11 to 1.64)  | .314 |
| 24                       |                       | −0.16 (−3.49 to 3.17)  | .926 | −0.09 (−3.34 to 3.25)  | .956 |
| 30                       |                       | −0.03 (−3.50 to 3.44)  | .985 | 0.03 (−3.46 to 3.52)  | .987 |
| 36                       |                       | 0.62 (−2.96 to 4.19)   | .736 | 0.71 (−2.92 to 4.34)  | .701 |
| No. of desaturations     | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | 2.19 (−1.35 to 5.73)  | .225 | 2.27 (−1.30 to 5.84)  | .213 |
| 12                       |                       | 1.66 (−1.92 to 5.24)  | .362 | 1.75 (−1.85 to 5.36)  | .340 |
| 18                       |                       | 3.90 (0.32 to 7.48)   | .033 | 3.96 (0.32 to 7.60)   | .033 |
| 24                       |                       | 5.33 (1.81 to 8.85)   | .003 | 5.37 (1.83 to 8.92)   | .003 |
| 30                       |                       | 3.80 (−0.07 to 7.63)  | .054 | 3.81 (−0.07 to 7.7)   | .054 |
| 36                       |                       | 3.15 (−0.7 to 6.1)    | .109 | 3.29 (−0.64 to 7.21)  | .101 |
| REM, %                   | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | 0.22 (−3.84 to 4.28)  | .916 | 0.19 (−3.89 to 4.27)  | .926 |
| 12                       |                       | −3.30 (−7.45 to 0.84) | .118 | −3.27 (−7.43 to 0.89) | .124 |
| 18                       |                       | −0.39 (−4.17 to 3.37) | .836 | −0.49 (−4.29 to 3.29) | .798 |
| 24                       |                       | 0.79 (−2.93 to 4.53)  | .674 | 1.06 (−2.69 to 4.820) | .578 |
| 30                       |                       | −0.33 (−4.29 to 3.61) | .866 | −0.17 (−4.13 to 3.79) | .933 |
| 36                       |                       | −1.36 (−5.35 to 2.62) | .502 | −1.07 (−5.13 to 2.97) | .602 |
| REM latency, min         | Baseline              | Reference     |       | Reference     |       |
| 6                        |                       | 11.1 (−23.80 to 46.00) | .533 | 10.15 (−25.03 to 45.34) | .572 |
| 12                       |                       | 26.31 (−8.20 to 60.82) | .135 | 24.94 (−9.88 to 59.76) | .160 |
| 18                       |                       | 8.98 (−25.51 to 43.48) | .610 | 9.69 (−25.32 to 44.70) | .587 |
| 24                       |                       | −18.56 (−52.68−15.56) | .286 | −19.66 (−54.05 to 14.73) | .263 |
| 30                       |                       | 4.56 (−31.82 to 40.93) | .806 | 3.63 (−33.00 to 40.31) | .845 |
| 36                       |                       | 11.66 (−23.97 to 47.30) | .521 | 9.70 (−26.52 to 45.92) | .600 |
Administration was notified that at least 7 children with PWS had died within a few months after initiating GH treatment. It was suspected that these deaths were caused by respiratory failure, but it was unclear how the known effects of GH could explain any causal relationship between GH replacement and respiratory failure and if the number of deaths reported represented an increase in the mortality rate. However, these children were treated with higher GH doses than used in the present study. Possible mechanisms could include sodium and water retention and fibroblast stimulation leading to soft-tissue swelling. Furthermore, the smaller diameter of the airways in children could make them more susceptible to airway obstruction.

In line with this, consensus guidelines for GH treatment in children with PWS recommend performing PSG before initiating GH treatment, especially in obese children, and to repeat PSG after 3 to 6 months of treatment. Moreover, the risk of GH inducing growth of adenotonsillar tissues, which can contribute to OSA, necessitates an ENT evaluation if OSA is diagnosed (4).

Studies investigating the effect of GH on SRBDs in children with PWS have shown that GH treatment does not negatively influence AHI (5, 10, 26-28). Much less is known about the effect in adults. Two studies investigated the effect of GH treatment on SRBDs in young adults; in both studies, 1 year of GH treatment improved AHI (29, 30). Another study showed that OSA in children with PWS developed independently of GH treatment onset during or after the first year of life (31). The authors concluded that GH treatment may safely be initiated early in life, but should be accompanied by regular sleep analysis.

In our study, SE improved during GH treatment, and the improvement was already seen after 6 months and continued throughout the study. The level of significance remained the same after adjustment for BMI, although no difference in SE was seen between placebo and GH treatment. This is an interesting finding. In a previous study of adults with PWS, frequent hypersomnolence was reported (5), and in another study moderate to severe OSA was found to result in an increased daytime sleepiness (8). An improvement in SE may reduce daytime sleepiness, and secondarily the emotional disturbances, and low attention spans frequently seen in PWS (32). It is well known that GH improves body composition and increases lean body mass, therefore GH treatment would be anticipated to improve respiration. Previously published data from the Scandinavian study reported improvement in lean body mass of 2.25 kg in the GH-treated group during the placebo-controlled treatment period (18). At year 2 lean body mass had increased 2.8 kg and lung function as evaluated by peak expiratory flow had increased 12%, indicating improved muscle function (19). It is interesting that the improvement in body composition was seen despite only a few patients fulfilling the criteria

### Table 3. Continued

| Outcome                  | Coef (95% CI)       | P     | Coef (95% CI)       | P     |
|--------------------------|---------------------|-------|---------------------|-------|
|                         | Baseline            |       | Reference           |       |
| Sleep efficiency, %      | 6                   | 2.80 (0.75 to 6.35) | .122  | 2.66 (–0.91 to 6.22) | .144  |
|                          | 12                  | 4.97 (1.44 to 8.49) | .006  | 4.79 (1.25 to 8.33) | .008  |
|                          | 18                  | 6.24 (2.66 to 9.83) | .001  | 6.12 (2.49 to 9.76) | .001  |
|                          | 24                  | 4.81 (1.22 to 8.40) | .009  | 4.79 (1.2 to 8.39)  | .009  |
|                          | 30                  | 7.04 (3.18 to 10.91)| .000  | 7.1 (3.20 to 10.96) | .000  |
|                          | 36                  | 6.64 (2.86 to 10.41)| .001  | 6.52 (2.69 to 10.36)| .001  |
| Delta sleep              | 6                   | –2.12 (–5.02 to 0.78)| .152  | –2.06 (–4.99 to 0.87)| .167  |
|                          | 12                  | 3.57 (0.62 to 6.52) | .018  | 3.63 (0.65 to 0.87) | .017  |
|                          | 18                  | 1.40 (–1.55 to 4.36)| .352  | 1.46 (–1.55 to 4.48)| .340  |
|                          | 24                  | 2.21 (–0.69 to 5.12)| .135  | 2.23 (–0.69 to 5.16)| .135  |
|                          | 30                  | 0.52 (–2.63 to 3.67)| .745  | 0.52 (–2.65 to 3.70)| .746  |
|                          | 36                  | 0.60 (–2.37 to 3.78)| .710  | 0.68 (–2.57 to 3.92)| .682  |
| IGF-1                    | 12                  | 24.65 (11.27-38.03) | .001  | 23.11 (11.78 to 38.46)| .001  |
|                          | 24                  | 64.78 (51.51 to 78.03)| .001  | 64.99 (51.79 to 78.20)| .001  |
|                          | 36                  | 63.07 (49.57 to 76.58)| .001  | 63.44 (49.78 to 77.01)| .001  |

**Abbreviations:** AHI, apnea hypopnea index; BMI, body mass index; Coef, coefficient; IGF-1, insulin-like growth factor 1; PLM, periodic limb movement; REM, rapid eye movement; SAT, oxygen saturation.

*Adjusted for BMI.
of adult GHD. Thus, all adults with PWS can benefit from GH treatment, not just those with documented GHD. One could speculate that GH treatment increases muscle strength, which would lead to less interrupted sleep (although not reflected in REM and delta sleep). This would increase SE, which in turn might explain the increase in length of longest apneas. However, the effect of adaptation (ie, individuals getting used to the examination) and thus, not an effect of the GH treatment, cannot be excluded.

The length of the longest apnea was significantly increased (last visit only) after receiving GH continuously for 3 years, and only after adjustment for BMI. Median AHI was normal at baseline, and after long-term GH treatment we found an insignificant increase in AHI and in the number of desaturations. The clinical relevance of these findings is uncertain. PSG is affected by many factors (age, BMI, drugs, mood, behavior, and compliance with examinations) that might appear or change over time and might explain the varying results. However, over the 3-year study period only small changes in body weight were noted, which probably did not influence the results of this study (27, 29). Also, the ENT examinations did not detect any increase in tonsillar size. Thus, because of the multifactorial etiology of SRBDs, continuous watchfulness for the development of SRBDs in adults with PWS with or without GH treatment is recommended.

It is important to treat SRBDs in adults with PWS to limit the risk of severe respiratory events during sleep and to prevent unintended health consequences. Over time, untreated OSA may lead to cardiovascular complications including hypertension, cor pulmonale, and stroke (17). In addition to long-term adverse cardiovascular and respiratory events associated with untreated OSA, sleep that is interrupted by respiratory events and arousals may cause daytime sleepiness, compromise cognitive function, and worsening of executive function and memory. These complications might be related to hypoxemia and sleep fragmentation (17). Prevention of obesity is the key to minimizing the risk of developing OSA, as well as to keeping metabolic parameters and blood pressure normal. OSA is treated with CPAP and tonsillectomy if tonsillar hypertrophy is causing OSA. Moreover, patients with PWS often suffer from sleepiness and different forms of hypersomnia disorders, and it is important to carefully investigate their sleep (8). In PWS leptin, ghrelin, and adiponectin are peptides associated with various degrees of nutritional states (33-35), and in future studies it would be of value to evaluate the relation between them and obesity and SRBD.

Strengths and Limitations
The strength of this study is its design of a double-blinded, placebo-controlled period of 1 year followed by an open-phase period of GH treatment for 2 years. This made it possible to evaluate GH's effects on respiratory and sleep parameters during the short and long term. Limitations of the study include the small number of participants, reducing detailed analyses of subgroups, and that there was no control group at 24 and 36 months. Also, intercurrent illnesses, including a few patients with tonsillitis during the study, might have influenced the results.

Conclusion
In the present study, no clinical, significant negative impact on respiration and sleep parameters as measured by PSG in adults with PWS was observed during short- or long-term GH treatment. SE improved, but on the other hand the length of the longest apnea and the number of desaturations inconsistently increased. The clinical relevance of these findings remains to be determined. In the literature, SRBDs are frequent in adults with PWS, but this was not documented in this study, maybe because the patients were less overweight. The etiology of SRBDs is multifactorial, and repeated sleep analysis should be considered in any adult with PWS with or without GH treatment. In summary, GH treatment of adults with PWS did not significantly impair sleep parameters and no deaths occurred. GH treatment of adults with PWS has many positive effects, and our study showed that GH treatment is safe and concerns of a negative impact on sleep-related parameters could not be confirmed. While further studies in this context are warranted, our results add to the confidence in GH treatment in adults with PWS.

Acknowledgments
Financial Support: This work was supported by Novo Nordisk Scandinavia AB, Malmö, Sweden, and Novo Nordisk, Bagsvärd, Denmark.
Clinical Trial Information: Clinical trial registration No. NCT00372125 (registered December 1, 2003).

Additional Information
Correspondence: Hasanain Hamid Shukur, MD, Department of Molecular Medicine and Surgery, Karolinska Institute, L1:00, Anna Steckens gata 53, Stockholm, Solna SE-171 76, Sweden. Email: hasanain.shukur@ki.se.
Disclosures: C.H. and A.P.J. were NordiNet investigators and have received lecture fees from NovoNordisk. S.F. has received lecture fees from NovoNordisk. The other authors have nothing to disclose.
Data Availability: Data are available on request from the corresponding author.
References

1. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10-26.

2. Angulo MA, Butler MG, CATALLETO ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Invest. 2015;38(12):1249-1263.

3. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93(11):4183-4197.

4. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS. 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013;98(6):E1072-E1087.

5. Miller J, Wagner M. Prader-Willi syndrome and sleep-disordered breathing. Pediatr Ann. 2013;42(10):200-204.

6. Sedky K, Bennett DS, Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. J Clin Sleep Med. 2014;10(4):403-409.

7. Gillett ES, Perez IA. Disorders of sleep and ventilatory control in Prader-Willi syndrome. Diseases. 2016;4(3):23.

8. Ghergan A, Coupaye M, Leu-Semenescu S, et al. Prevalence and phenotype of sleep disorders in 60 adults with Prader-Willi syndrome. Sleep. 2017;40(12):zsz162.

9. de Lind van Wijngaarden RF, Joosten KE, van den Berg S, et al. The relationship between central adrenal insufficiency and sleep-related breathing disorders in children with Prader-Willi syndrome. J Clin Endocrinol Metab. 2009;94(7):2387-2393.

10. Van Vliet G, Dea CL, Crock PA, Robitaile Y, Oligny LL. Sudden death in growth hormone-treated children with Prader-Willi syndrome. J Pediatr. 2004;144(1):129-131.

11. Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK health region. J Med Genet. 2001;38(11):792-798.

12. Schrander-Stumpel C, Sijtemans H, Curfs L, Fryns JP. Sudden death in children with Prader-Willy [sic] syndrome: a call for collaboration. Genet Couns. 1998;9(3):231-232.

13. Whittington JE, Holland AJ, Webb T. Ageing in people with Prader-Willi syndrome: mortality in the UK population cohort and morbidity in an older sample of adults. Psychol Med. 2015;45(3):615-621.

14. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol. 2002;44(4):248-253.

15. Nagai T, Obata K, Tonoki H, et al. Cause of sudden, unexpected death of Prader-Willi syndrome patients with or without growth hormone treatment. Am J Med Genet A. 2005;136(1):45-48.

16. Tauber M, Diene G, Molinas C, Hébert M. Review of 64 cases of death in children with Prader-Willi syndrome (PWS). Am J Med Genet A. 2008;146A(7):881-887.

17. Zhao X, Li X, Xu H, et al. Relationships between cardiometabolic disorders and obstructive sleep apnea: implications for cardiovascular disease risk. J Clin Hypertens (Greenwich). 2019;21(2):280-290.

18. Rosenberg AGW, Pellikaan K, Poitou C, et al. Central adrenal insufficiency is rare in adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2020;105(7):e2563-e2571.

19. Sode-Carlsen R, Farholt S, Rabben KE, et al. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2010;95(11):4943-4950.

20. Sode-Carlsen R, Farholt S, Rabben KE, et al. Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. Growth Horm IGF Res. 2011;21(4):185-190.

21. Sode-Carlsen R, Farholt S, Rabben KE, et al. Growth hormone treatment in adults with Prader-Willi syndrome: the Scandinavian study. Endocrine. 2012;41(2):191-199.

22. Berry RB, Budhiraja R, Gottlieb DJ, et al; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619.

23. Iber C, Ancoli-Israel S, Chessor AL Jr, Quan SF. The new sleep scoring manual—the evidence behind the rules. J Clin Sleep Med. 2007;3(2):107-122.

24. Mitterling T, Hölgl B, Schönwald SV, et al. Sleep and respiration in 100 healthy Caucasian sleepers—a polysomnographic study according to American Academy of Sleep Medicine standards. Sleep. 2015;38(6):867-875.

25. Boulos MI, Jairam T, Kendzerska T, Im J, Mekhael A, Murray BJ. Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(6):533-543.

26. Frystyk J, Dinesen B, Orskov H. Non-competitive time-resolved immunofluorometric assays for determination of human insulin-like growth factor I and II. Growth Regul. 1995;5(4):169-176.

27. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. J Clin Endocrinol Metab. 2006;91(2):413-417.

28. Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC. Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. J Clin Endocrinol Metab. 2006;91(12):4911-4915.

29. Tan HL, Urquhart DS. Respiratory complications in children with Prader Willi syndrome. Paediatr Respir Rev. 2017;22:52-59.

30. Donze SH, de Weerd AW, van den Bossche RAS, Joosten KFM, Hokken-Koelega ACS. Sleep-related breathing disorders in young adults with Prader-Willi syndrome: a placebo-controlled, cross-over GH trial. J Clin Endocrinol Metab. 2019;104(9):3931-3938.

31. Zimmermann M, Laemmer C, Woelfle J, Fimmers R, Gohlke B. Sleep-disordered breathing in children with Prader-Willi syndrome in relation to growth hormone therapy onset. Horm Res Paediatr. 2020;93(2):85-93.
32. Feighan SM, Hughes M, Maunder K, Roche E, Gallagher L. A profile of mental health and behaviour in Prader-Willi syndrome. *J Intellect Disabil Res*. 2020;64(2):158-169.

33. Höybye C, Barkeling B, Espelund U, Petersson M, Thorén M. Peptides associated with hyperphagia in adults with Prader-Willi syndrome before and during GH treatment. *Growth Horm IGF Res*. 2003;13(6):322-327.

34. Tauber M, Coupaye M, Diene G, Molinas C, Valette M, Beauloye V. Prader-Willi syndrome: a model for understanding the ghrelin system. *J Neuroendocrinol*. 2019;31(7):e12728.

35. Höybye C, Bruun JM, Richelsen B, Flyvbjerg A, Frystyk J. Serum adiponectin levels in adults with Prader-Willi syndrome are independent of anthropometrical parameters and do not change with GH treatment. *Eur J Endocrinol*. 2004;151(4):457-461.